DISSERTATIONES SCHOLAE DOCTORALIS AD SANITATEM INVESTIGANDAM
UNIVERSITATIS HELSINKIENSIS

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SMALL CHOROIDAL MELANOMAS — MANAGEMENT AND PROGNOSIS

DEPARTMENT OF OPHTHALMOLOGY
HELSINKI UNIVERSITY HOSPITAL
AND
FACULTY OF MEDICINE
DOCTORAL PROGRAMME IN CLINICAL RESEARCH
UNIVERSITY OF HELSINKI

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Helsinki, Finland

SMALL CHOROIDAL MELANOMAS

MANAGEMENT AND PROGNOSIS

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nee Salkola

DOCTORAL DISSERTATION

To be presented, with the permission of the Faculty of Medicine,
University of Helsinki, for public examination in Lecture Hall 1 of
the Haartman Institute, Haartmaninkatu 3, on December 18, 2020, at 12 noon.

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Dissertitationes Scholae Doctoralis Ad Sanitatem Investigandam Universitatis Helsinkiensis
ISBN 978-951-51-6689-0 (pbk.)
ISBN 978-951-51-6690-6 (PDF)
ISSN 2342-3161 (pbk.)
ISSN 2342-317X (PDF)

Layout: Tinde Päivärinta/PSWFolders Oy/Ltd
Hansaprint, 2020, Vantaa, Finland

To Lauri, Kaarlo, and Okko

"*It is not the ship so much as the skilful sailing*
that assures the prosperous voyage"

George William Curtis

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1. List of original publications

This thesis is based on the following publications:

I Salkola S, Heikkonen J, Eskelin S, Kivelä T,. Management of choroidal melanomas less than 10 mm in largest basal diameter with a 10-mm ruthenium^{106} plaque. Retina. 2014; 34:2110-20.

II Jouhi S, Reijonen V, Heikkonen J, Raivio V, Täll M, Kivelä T,. Brachytherapy of choroidal melanomas less than 10 mm in largest basal diameter: Comparison of 10-mm and 15-mm ruthenium^{106} plaques. Ophthalmology. 2020; [Online ahead of print]

III Jouhi S, Jager M, de Geus S, Desjardins L, Eide N, Grange J, Kiilgaard J, Seregard S, Midena E, Parrozzani R, Caujolle J, Rospond-Kubiak I, Kivelä T,. The small fatal choroidal melanoma study: A survey by the European ophthalmic oncology group. American Journal of Ophthalmology. 2019; 202:100-8.

IV Jouhi S, Al-Jamal R, Täll M, Eskelin S, Kivelä T,. Presumed incipient choroidal melanoma: Diagnostic criteria and management with transpupillary thermotherapy. [Submitted for publication]

The original publications are referred to in the text by their Roman numerals. They are reprinted in this thesis with the permission of the copyright holders.

2. Abbreviations

AJCC	American Joint Committee on Cancer
BAP1	BRCA-associated protein-1
BCVA	Best corrected visual acuity
BRCA	Breast cancer gene
CCA	15-mm round radioactive plaque
CCX	10-mm round radioactive plaque
CI	Confidence interval
CM	Choroidal melanoma
COMS	Collaborative Ocular Melanoma Study
CPI	Checkpoint inhibitor
CT	Computed tomography
DD	Disc diameter (about 1.5 mm)
DT	Doubling time
EDI	Enhanced depth imaging
FAF	Fundus autofluorescence
FAG	Fluorescein angiography
GEP	Gene expression profile
HPF	High power field
I^{125}	Iodine^{125} isotope
ICGA	Indocyanine green angiography
IOP	Intraocular pressure
LBD	Largest basal diameter
LFT	Liver function test
MBD4	Methyl-CpG-binding domain 4
MRI	Magnetic resonance imaging
OCT	Optical coherence tomography
OOG	Ocular Oncology Group
OP	Orange pigment
Pd^{103}	Palladium^{103} isotope
PRAME	Preferentially expressed antigen in melanoma
RPE	Retinal pigment epithelium
Ru^{106}	Ruthenium^{106} isotope
SD	Standard deviation
SE	Standard error
SFCM	Small fatal choroidal melanoma
SRF	Subretinal fluid
SS	Swept source
TDT	Tumour doubling time
TNM	Tumour, Node, Metastasis classification
TTT	Transpupillary thermotherapy
UM	Uveal melanoma
US	Ultrasound
WHO	World Health Organization

3. Abstract

The first part of this thesis summarizes the current literature on small choroidal melanomas (CMs). Although the aetiology of this disease remains unknown, many risk factors have been reported. Differentiation from the more common choroidal naevi is generally clinical, and several typical characteristics of the malignant tumour have been used as a diagnostical tool. When the differentiation cannot be made clinically or by biopsy, the remaining option is to observe for growth that signals malignancy.[1-3] Small posterior tumours, in particular, have frequently been observed for growth because treatment would most likely affect vision. However, observation before treatment might increase the risk for metastases.[4]

Small CMs are typically treated conservatively, and enucleation is no longer a generally accepted alternative, partly because these tumours are thought to be able to micrometastasise years before diagnosis.[5] The primary aims when managing small malignant CMs are to destroy the tumour and prevent local recurrences that might be associated with an increased risk for metastases.[6-8] Eye-preserving treatments frequently allow for the preservation of useful vision as well. Several options are available for treating small CMs. In Finland, the majority of CMs are treated with episcleral plaque brachytherapy. Ruthenium[106] brachytherapy is an effective choice for small melanomas because the dose distribution is ideal for treating tumours with a thickness of up to 5.4 mm.[9]

The second and main part of this thesis summarizes the recent Finnish contributions to this field. The research presented in this thesis starts by retrospectively examining the treatment results from 10-mm ruthenium plaque (Study I), leading to a comparative study looking at the treatment results of both 10-mm round radioactive plaque (CCX) and 15-mm round radioactive plaque (CCA), with the aim to see whether and when it is safe to reduce vision-threatening radiation side-effects by using a smaller plaque (Study II) when treating small CMs less than 10 mm in their largest basal diameters (LBDs). The smallest 10-mm plaque delivers less scattered radiation compared with a 15-mm plaque or larger. Previously, it was not known whether a smaller radiation area and less scattered radiation could affect the recurrence rate, preservation of useful vision, and frequency of side-effects. This thesis found that the recurrence and complication rates were comparable between patients treated with the 10-mm or 15-mm plaque, but vision was more effectively preserved after treatment with the 10-mm plaque when the tumour was located close to the foveola. An eccentric location of the plaque was a risk factor for a local recurrence with both plaques. This study supports the treatment of small posterior CMs close to fovea with 10-mm rather than 15-mm plaque.

The challenge of diagnosing small CMs before they have the capacity to disseminate led to the search for the smallest size of a CM that had been reported to metastasize and an attempt to find out whether melanomas that disseminated and melanomas that did not

disseminate differed from each other clinically. As the Finnish population is not sufficiently large to collect data for this study, a retrospective collaboration study was done with the European Ocular Oncology Group (OOG) (Study III). Ten ocular oncology services submitted the data on all their patients with a CM of 3 mm or less in thickness and 9 mm or less in LBD who were treated and who subsequently developed metastases. This study found that CMs less than 3 mm in LBD are unlikely to metastasize. Observation without treatment beyond this limit might impair survival. Clinical characteristics of small fatal choroidal melanomas (SFCMs) did not differ from those of non-fatal CMs of a similar size: clinical characteristics predicting metastasis could not be identified.

Due to inspiration from Study III, ways to alternatively diagnose small melanomas before they get the capacity to disseminate were examined. The growth rates and tumour doubling times (TDT) of incipient CMs were calculated (Study IV). Short TDT and a fast growth rate combined with the calculated age at tumour origin after puberty supported a melanoma diagnosis. These were the nine smallest presumed CMs reported at that point. The earlier diagnosis enabled treating these patients with less invasive transpupillary thermotherapy (TTT), of which preliminary results are shared in this thesis. The reported growth parameters could be employed as diagnostic criteria for the incipient melanomas.

4. Summary in Finnish

Tämän väitöskirjan ensimmäinen osa kokoaa kirjallisuuskatsaukseksi suonikalvon melanoomaa käsittelevät ajankohtaiset julkaisut. Vaikka suonikalvon melanooman etiologia on avoin, monia sille altistavia tekijöitä tunnetaan. Melanooman erottaminen yleisemmästä hyvänlaatuisesta luomesta tapahtuu useimmiten kasvaimen kliinisten piirteiden perusteella. Jos kasvaimen pahanlaatuisuutta ei voida kliinisten piirteiden tai biopsian avulla varmentaa, kasvainta seurataan mahdollisen kasvun havaitsemiseksi.[1-3] Erityisesti pieniä silmän takaosassa sijaitsevia kasvaimia seurataan diagnoosin ollessa epävarma, sillä hoito todennäköisimmin heikentää näköä. Kasvainten seuraaminen ennen hoitoa voi suurentaa riskiä etäpesäkkeille.[4]

Pienet suonikalvon melanoomat hoidetaan tavallisesti paikallisesti eikä silmänpoisto ole enää yleisesti hyväksytty hoitokäytäntö, koska näiden syöpäkasvainten ajatellaan olevan leviämiskykyisiä jo vuosia ennen diagnoosia.[5] Hoidon tärkein tavoite on tuhota kasvain ja estää kasvaimen paikallinen uusiutuma, mikä itsessään on riski etäpesäkkeille.[6-8] Silmän säästävä hoito voi myös mahdollistaa käyttökelpoisen näkökyvyn säilyttämisen. Useista hoitovaihtoehdoista Suomessa on yleisimmin käytössä kovakalvon pinnalle asetettava sädehoitolevy. Rutenium^{106}-isotooppi soveltuu hyvin alle 5.4 mm paksujen kasvainten hoitoon ideaalisen annosjakaumansa vuoksi.[9]

Tämän väitöskirjan toinen osa kokoaa viimeisimmät suonikalvon melanoomien diagnostiikkaa ja hoitoa käsittelevät kotimaiset julkaisut yhdeksi kokonaisuudeksi. Tässä väitöskirjassa esitetty tutkimus alkoi hoitotuloksien selvityksellä, jossa pienten alle 10 mm halkaisijaltaan olevien kasvainten hoitoon oli käytetty 10-mm halkaisijaltaan olevaa ruthenium-sädehoitolevyä (osatyö I). Tutkimusta jatkettiin tekemällä vertaileva työ 10 mm (CCX) ja 15 mm sädehoitolevyillä (CCA) saaduista hoitotuloksista (osatyö II). Pienemmän halkaisijaltaan 10 mm levyn tavoitteena on säästää näkökykyä, koska pienemmän säteilevän alueen lisäksi pienempi levy tuottaa puolet vähemmän hajasäteilyä. Aiemmin ei ollut tiedossa vaikuttaako pienempi sädehoidettava alue ja pienempi hajasäteilyn määrä hoitotuloksiin niin kasvaimen uusiutumisen kuin näkökyvyn säilymisenkin suhteen. Paikallisissa kasvainten uusiutumisissa tai hoitoon liittyvissä komplikaatioissa ei havaittu eroa ryhmien välillä, mutta näkökykyä onnistuttiin säilyttämään hieman paremmin, kun hoitoon valittiin 10 mm levy. Tämä tutkimus suosittelee pienten silmän takaosassa sijaitsevien alle 10 mm halkaisijaltaan olevien kasvaimien hoitoon 10 mm halkaisijaltaan olevaa levyä.

Pienten suonikalvon melanoomien hoidon haasteena on diagnosoida pahanlaatuiset kasvaimet ennen kuin ne saavuttavat leviämiskyvyn. Asian selvittämiseksi käynnistettiin monikeskustutkimus, jossa 10 eurooppalaista silmäkasvaimia hoitavaa keskusta lähetti tiedot alle 3 mm paksuista ja alle 9 mm halkaisijaltaan olevista suonikalvon melanoomista,

jotka olivat lähettäneet etäpesäkkeitä. Aineistosta selvitettiin pienimmän etäpesäkkeitä lähettäneen suonikalvon melanooman koko ja etäpesäkkeitä lähettäneiden kasvainten kliinisiä piirteitä verrattiin kasvaimiin, jotka eivät olleet levinneet. Tulosten perusteella alle 3 mm halkaisijaltaan olevat kasvaimet eivät todennäköisesti vielä lähetä etäpesäkkeitä. Kasvavan muutoksen seuranta tämän raja-arvon jälkeen voi altistaa potilaan etäpesäkkeille. Kasvainten kliinisten piirteiden perusteella ei voi arvioida etäpesäkkeiden kehittymisen riskiä.

Selvitystä siitä, onko suonikalvon melanoomat mahdollisesta diagnosoida ennen kuin ne saavuttavat leviämiskyvyn jatkettiin. Joukko pieniä suonikalvon muutoksia, jotka ovat nopean kasvutaipumuksensa vuoksi todennäköisimmin melanoomia analysoitiin. Muutosten kasvunopeudet ja kahdentumisajat laskettiin ja kasvunopeuden perusteella arvioitiin potilaan ikä, jolloin kasvain olisi ollut havaittavissa. Nopeat kasvunopeudet ja kahdentumisajat verrattuna hyvänlaatuisiin luomiin ja laskennallinen ikä luomien havaitsemiselle aikuisiällä tukevat melanomadiagnoosia. Aiempaa varhaisempi diagnoosi mahdollistaa potilaiden hoitamisen transpupillaarisella lämpölaserhoidolla sädehoidon sijaan, jolloin voidaan välttyä säteilyn aiheuttamilta haittavaikutuksilta. Raportoitua tapaa mitata kasvunopeutta voidaan käyttää pienimpien suonikalvon melanoomien diagnostiikan apuna.

5. Introduction

Uveal melanoma (UM) is the second most common intraocular malignancy after retinoblastoma worldwide but the most common in Caucasians and adults.[10-14] Up to one half of patients with UM develop metastatic disease within 10 years of diagnosis[15-21], and the median survival after metastases has ranged from 6 to 13 months.[19,22,23] Early diagnosis and treatment of UM are crucial because a larger size impairs prognosis.[14,24-30] However, differentiation between benign naevi and small malignant CM can be difficult, as there is a spectrum of small choroidal melanocytic lesions ranging from benign lesions – naevi – with minor growth potential and no clinical risk factors to obviously malignant lesions with documented growth, several risk factors, and significant risk for metastatic disease.[29,31,32] Management of small choroidal tumours is further complicated by the small number of naevi that transform into cancer.[26,29,33]

Treatment of low-risk small choroidal melanocytic lesions is controversial because the significant majority of such tumours tend to remain stable and are likely benign choroidal naevi that will not spawn a melanoma during the lifetime of the patient.[1,34-38] Certain clinical factors have been shown to predict growth that helps clinicians to distinguish small CMs from benign lesions.[28,29,31,32,39-41] Such factors include, in particular, tumour thickness over 2 mm, subretinal fluid (SRF), symptoms, orange pigment (OP), and the margin either touching or being within 2 disc diameters (DD) of the optic disc.[27,42] When risk factors are lacking, these tumours are followed-up in order to detect growth to ascertain malignancy and to justify treatment.[34] Particularly small posterior tumours are frequently observed for growth because treatment will most likely compromise vision. Tumour growth over a short period is considered a hallmark of CM although benign choroidal naevi can demonstrate slow growth over a period of many years to several decades as well, and the presence of such a slow growth in the absence of other risk factors is not an indicator for treatment.[43]

Follow-up without treatment may theoretically have an effect on prognosis and expose the patient to metastatic disease if the tumour is a melanoma.[4] The dilemma is that, while potentially malignant tumours that can spread systemically should be treated without delay, their identification can be challenging. Additionally, treatment of benign tumours does not benefit the patient and will likely deteriorate the patient's vision. The goal is to identify and only treat melanocytic lesions that are likely to spread to thus destroy these lesions before they do so.

A majority of CMs are treated conservatively either with episcleral plaque radiotherapy alone or in combination with TTT.[44-50] Enucleation does not improve prognosis because tumours that have the capacity to disseminate are estimated to micrometastasise years before diagnosis.[5] The primary goals in the management of small malignant melanomas are to destroy the tumour and to prevent local recurrences that might be associated

with an increased risk for metastases.[6,51] Conservative treatment frequently allows for the preservation of useful vision. However, small CMs are frequently located posteriorly where the risk of vision loss is higher because of treatment side-effects. Tumours must be effectively treated to a sufficient degree to prevent local and systemic recurrence, simultaneously minimizing toxicity to healthy tissues.

In TTT, 810 nm diode laser energy is directed through a dilated pupil to the tumour apex, causing hyperthermia.[48] As a primary treatment TTT is controversial because of high local recurrence rates.[52-60] It could be a treatment of choice in a selected group of patients with small choroidal tumours with minimal risk factors located close to but outside the central macula.[53,61]

The research behind the present thesis aimed to determine the size limit of a small choroidal melanoma becoming capable of dissemination, describe the clinical tumour characteristics of metastasizing small tumours, and report TDTs and growth rates of incipient tumours in order to discover diagnostic criteria that could establish when small pigmented tumours should be treated. This thesis futher reports the results of treatment with primary Ru^{106} brachytherapy using 10-mm and 15-mm plaques and presents the comparison between the two plaque types to find the safest and most efficient treatment technique for small choroidal CMs.

6. Review of the literature

6.1. OVERVIEW OF CHOROIDAL MELANOMA

6.1.1. Epidemiology

The incidence of UM varies by race, latitude, age, and gender. It predominantly affects white Caucasians.[62-64] The mean age-standardized incidence rate is 5.1 cases per million per year.[15] The incidence rate varies inside Europe, with the highest being in Northern Europe at approximately 8–9.5 per million and, in Finland, as high as 12 per million[65], as compared to 4–6 million in Central Europe and 1.7–2 per million in Southern Europe.[66,67] In the United States and Canada, the mean incidence rate is 4–6 per million,[14,15,62,68,69] with the highest incidence rate occurring in non-Hispanic whites at 6 per million as compared to black Americans and Asians at 0.3 and 0.4 per million, respectively.[70] The incidence rate in Australia is as high as in Northern Europe at 8 per million.[71] Standardized incidence rate estimates suggest that 7,000 new patients are diagnosed annually worldwide.[66] The standardized incidence of UM has remained stable over the years[14,15,20,72,73] in contrast with the rising incidence of cutaneous[74] and conjunctival melanoma[75]. However, the incidence of UM in Finland has increased in 20 years from approximately 8 to 12 per million due to an increasing overall population age.[65,67] The incidence rate increases with age, peaks at the age of 70[10-12], and plateaus after 75 years of age[12,14,15,66]. The median age range at diagnosis is 59–62 years.[12,15,64,76] The median age slowly increased over the years to 62 years due to increasing life expectancy.[77] The incidence of UM in children and teenagers is rare[78-80] and increases steadily until the age of 11 years, followed by a transition to a more than 10-times faster increase after the age of 17.[81] Males show a slight predominance in crude incidence.[10,64,67]

6.1.2. Pathogenesis

The aetiology of UM is unknown.[63] However, five driver mutations have been commonly found: BAP1, GNAQ, GNA11, SF3B1, and EIF1AX.[82-89] UMs originate from neuroectodermal melanocytes in the middle, uveal layer of the eye wall.[90] UMs are divided into different types according to their location: anteriorly located iris melanomas and posteriorly located ciliary body melanomas and CMs. The majority of UMs originate in the choroid (85%–90%), and remainder originate in the iris (3%–5%) and the ciliary body (5%–8%).[67,76,91,92]

UMs, although also originating from melanocytes, differ from cutaneous melanoma and mucous membrane – including conjunctival – melanomas in terms of epidemiology, aetiology, biology, genetics, and clinical features, including a high propensity to metastasize haematogenously to the liver.[93] UM predominantly disseminates haematogenously because there is no traditional lymphatic drainage within the eye.[94]

6.1.3. Host- and environment-related characteristics

Several predisposing factors have been identified as affecting the occurence of UM, including, as aforementioned, race, age, and gender and additionally including blue eyes, fair skin, the inability to tan, ocular or oculodermal melanocytosis, choroidal naevi, and germline mutations in BAP1 or MBD4 genes.

Although light skin and a blue iris colour are established risk factors for UM[95], the role of sun exposure is weak,[63,96,97] in contrast to cutaneous melanoma.[98] Long-term exposure to ultraviolet-radiation is not associated with the incidence of UM,[99] whereas intermittent exposure to ultraviolet rays from welding has been reported to double the risk of the development of UM,[99,100] this finding is, however, questionable.[101]

Congenital ocular melanocytosis is an important condition predisposing individuals to UM.[102] It is a rare developmental pigmentary disorder in which the number of melanocytes is increased in ocular and periocular tissues. Melanomas arising from ocular melanocytosis are associated with more frequent genomic alterations and a double risk for metastatic disease.[103,104]

Choroidal naevi carry a small risk of transformation into CM.[27-29,31,32,39-41,105-107] At least one in 10 melanomas originates from pre-existing naevi,[108-110] which, however, exist in approximately 3–8% of the general population.[25,26,111,112] The annual rate for malignant transformation is estimated at one in 3,664 to 8,845,[26,113] and the lifetime risk for malignant transformation is about 1%.[107]

Although UM generally occurs sporadically,[63] BAP1 germline mutations have been described in families with hereditary BAP1 cancer syndrome, including UM, comprising 0.6–6 % of UM patients depending on age.[114-124] The prevalence of pathogenic BAP1 variants is reported to be 25% in Finnish familial UMs.[125] Patients with BAP1 cancer syndrome have an increased risk of several cancers, the most frequent of which is UM.[82,115,117] Patients with UM have over 10% risk for other malignancies, which is, to a certain extent, driven by the presence of germline BAP1 mutations.[126]

UMs are associated with a predisposing germline loss-of-function variant in the MBD4 gene causing hypermutated tumours[127-129], a variant which has a prevalence in UM patients that is 9.15 times more frequent than in the general population.[127] These hypermutated tumours should be recognized since they may respond to checkpoint inhibitor (CPI) immunotherapy.[118,130-132]

6.1.4. Growth patterns

Small choroidal tumours are frequently flat or crescent in shape. After growing vertically, they become dome-shaped, and when the Bruch's membrane ruptures, they extend into the subretinal space and become mushroom-shaped.[90,133] The sclera presents resistance to the tumour expansion, and the tumour therefore protrudes into the vitreous cavity.[134] CMs may eventually extend through existing scleral channels along nerves and vessels into the episclera or the orbit, an event which occasionally occur, even with small choroidal tumours around the optic disc,[135-139] an area that is rich with intrascleral nerves and vascular channels.[134,140,141]

6.1.5. Classification of small choroidal melanoma

Numerous definitions have been devised for each CM size category.[18,142] The use of classifications should allow for the comparison of treatments for equivalently sized and staged tumours. The Collaborative Ocular Melanoma Study (COMS) has defined a small CM as being 1–2.5 mm in thickness and 5–16 mm in LBD; tumours smaller than this are regarded as probable naevi.[143] It has been estimated that when the LBD is 5–6 mm, about 70 choroidal naevi are diagnosed for each melanoma, and it has been stated that few melanomas would be less than 5 mm in diameter.[33,144]

UMs have been classified by size and anatomic extent which affect the risk for metastases and survival.[24] According to the American Joint Committee on Cancer (AJCC) Tumour, Node, Metastasis (TNM) staging systems latest 7th and 8th edition,[145,146] the criteria of tumour size caterory T1 are a thickness less than 3.0 mm if the LBD is less than 12.0 mm or a thickness less than 6.0 mm if the LBD is less than 9.0 mm. Tumour size category T2 tumours can be classified as medium-sized, and the corresponding size criteria are a thickness less than 3 mm if the LBD is 12.1–18 mm, a thickness of 3.1–6 mm if the LBD is 9.1–15 mm or a thickness 6.1–9 mm if the LBD is 9.1–12 mm. [145]

Table 1. Current Tumour, Node, Metastasis categorization of choroidal and ciliary body melanomas according to anatomical extent by the American Joint Committee on Cancer [145]

T1	**Tumour Size Category 1**
T1a	T1 category without ciliary body involvement or extraocular extension
T1b	T1 category with ciliary body involvement
T1c	T1 category without ciliary body but with extraocular extension 5 mm
T1d	T1 category with ciliary body and extraocular extension 5 mm
T2	**Tumour Size Category 2**
T2a-d	T2 category and similar sub-categories as for T1
T3	**Tumour Size Category 3**
T3a-d	T3 category and similar sub-categories as for T1
T4	**Tumour Size Category 4**
T4a-d	T4 category and similar sub-categories as for T1
T4e	Any tumour size category with extraocular extension > 5 mm

6.2. DIAGNOSIS

6.2.1. Diversity of small choroidal lesions

The difficulty of detecting small CM relates to the diversity of small pigmented choroidal lesions ranging from benign naevi, via indeterminate pigmented lesions, to malignant melanoma.[28,31,32,147] Clinical risk factors help clinicians to determine which small melanocytic choroidal tumours should be treated or biopsied without waiting for tumour growth. Lesions carrying any of these risk factors are generally referred for evaluation by a retinal specialist or ocular oncologist. Smaller melanomas typically show fewer risk factors than larger melanomas, making their diagnosis more difficult.[133]

There is no consensus on indications for treatment of small choroidal melanocytic tumours. The more risk factors are present, the more likely it is that a choroidal lesion is a melanoma.[148] Lesions that display one risk factor have a 38% risk for growth, and those with two or more factors show growth in over 50% of tumours.[148] When a lesion does not have any of these factors, the risk for growth and malignancy over 5 years is approximately 3%, and the tumour is more likely to be a choroidal naevus that can be monitored periodically.[148] However, the typical risk factors[27,42] are not pathognomocic for malignancy.[149] The treatment of low-risk small choroidal lesions is controversial because a majority of these lesions will remain stable and likely be benign choroidal naevi.[2,28,31,53]

6.2.2. Clinical risk factors for choroidal melanoma

Certain clinical signs are risk factors for tumour growth and metastasis.[27,31,32,39-42,150] These independent risk factors are a tumour thickness over 2 mm, a LBD over 5 mm, SRF, ocular symptoms, OP, a posterior tumour marging either touching or located within 3 mm of the optic disc, ultrasound (US) hollowness, the absence of a halo around the tumour, and the absence of drusen (Fig. 1).

A tumour thickness over 2 mm (Fig. 1) is a consistent independent risk factor for malignancy[27-29,33,150] and is associated with the class 2 gene expression profile (GEP)[149] (see below – 6.3.3: Cytogenetic prognosticators). Tumours less than1.0 mm in thickness are most likely naevi[27] and there are approximately 125 naevi for each melanoma in the thickness range between 1.5–2 mm, but only 25 naevi for each melanoma in the range of 2–2.5 mm, and 5 in the range of 2.5–3 mm.[144] The rate of melanoma-related metastasis at 10 years gradually increases by each millimetre from 6% to 51% when thickness increases from the 0–1.0mm to >10.0mm, respectively.[76] Additionally, a tumour diameter over 5 mm has been described as an independent risk factor for malignancy.[150]

Clinically detectable SRF (Fig. 1) is a strong indicator of metabolic activity and malignancy.[27,151] Optical coherence tomography (OCT) evidence of SRF has a predictive value in identifying tumours that have cellular activity and are likely to grow. However,

around 10% of choroidal naevi have been reported to present small amounts of SRF detectable on OCT due to the gradual atrophy of the retinal pigment epithelium (RPE) and loss of its pumping action that normally keeps the subretinal space dry.[64,150,152-155]

Small choroidal tumours can cause visual symptoms when located close to or extending under the fovea (Fig. 1). Since UMs are generally slowly growing tumours,[20,156] these symptoms are generally not specific. The most commonly presenting symptoms are blurred vision, photopsia, floaters, a visual field defect, and metamorphopsia.[27,108] The development of symptoms is frequently indicative of growth and frequently leads to the diagnosis of melanoma.[157]

The RPE can display intracellular lipofuscin accumulation overlying active tumours (Fig. 1).[158,159] This is clinically evident with biomicroscopy or fundus autofluorescence (FAF) of the posterior pole and is described as OP over the pigmented lesions. OP appears black over amelanotic tumours. OP can be found in over 6–10% of benign posteriorly located naevi, which should be frequently evaluated for malignancy; thus, the presence of OP alone does not automatically indicate malignancy.[105]

A posterior tumour margin either touching or extending within 2 DD from the optic disc margin has been associated with a higher risk for malignancy.[27,42] However, this location was reportedly no longer a significant risk factor when the analysis was based on multimodal imaging.[33]

Small CMs typically have a relatively low acoustic reflectivity on A- and B-scan US due to their homogenous regular structure (Fig. 1).[160-162] Additionally, a regular acoustic internal structure and the presence of a vascularity within the lesion can be detected.[160,163] These are useful when differentiating between choroidal metastases and haemangiomas.[164] B-scan US is additionally instrumental in measuring tumour thickness and the LBD, as well as in exploring tumour shapes and the presence of an extrascleral extensions.[133,165] Extraocular extensions of CM, which are rare in small melanomas,[166] appear as echolucent nodules adjacent to the sclera at the tumour base.[133] Choroidal naevi are frequently excessively thin to be reliably evaluated with US and do not facilitate the diagnosis of thin melanomas less than 1 mm in thickness either.[133]

The absence of a halo or overlying drusen are risk factors for growth.[42] A halo is a ring of lighter pigmentation surrounding a choroidal lesion. This phenomenon is generally associated with naevi but can occasionally be seen with melanomas.[167] Drusen are an age-related sign of a compromised RPE that have developed over a long period of time. Drusens can be seen overlying choroidal lesions and are the signal of inactive, and therefore most likely benign, naevi. Drusen do not exclude the possibility of malignancy. They may occasionally suggest that a previous naevus has become active, particularly when they are unevenly distributed over the lesion.[105] Drusen can additionally be an incidental finding

over a choroidal tumour when they are further present in the surrounding retina as an age-related degeneration.

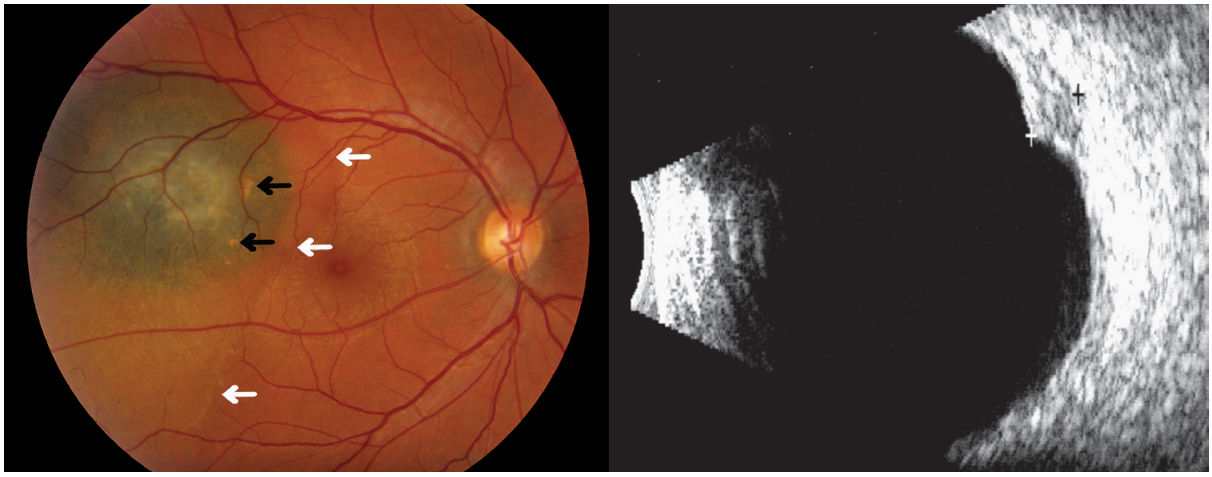

Figure 1. A small choroidal melanocytic tumour with 4 clinical risk factors: symptoms (metamorphopsia and a visual field defect), on ophthalmoscopy (**Left):** subretinal fluid (SRF) (white arrows), and orange pigment (OP) (black arrows), and on B-scan ultrasonography (**Right):** a tumour thickness over 2 mm, as well as a relatively hollow internal reflectivity.

6.2.3. Clinical diagnosis

Clinical risk factors are most frequently evaluated by comprehensive ophthalmic examination, US, OCT, and in the case of indeterminate tumours, by serial observations for tumour growth as well. Other available methods for diagnostic verification are different modalities of OCT, fluorescein angiography (FAG), indocyanine green angiography (ICG), and FAF. For small tumours, computed tomography (CT) or magnetic resonance imaging (MRI) is generally not needed unless an extrascleral extension or optic nerve invasion are suspected.

OCT and optical coherence tomography angiography (OCTA) are non-invasive imaging modalities that provide a more detailed image of the retina and choroid when compared to US.[168] OCTA provides insight into retinal vascular abnormalities related to CMs, such as an enlargement of the deep foveal avascular zone and a decrease in the superficial and deep parafoveal capillary vascular densities, which appear to be correlated with the presence of SRF and to be absent in choroidal naevi.[168,169] OCT technology is traditionally limited to the examination of posterior lesions, but newer technologies enable a view of peripheral lesions as well.[170] Furthermore, a microscope-integrated OCT has been used intra-operatively to guide a biopsy in real-time, increasing the chance of obtaining an adequate sample and avoiding unnecessary damage.[171]

Enhanced depth imaging optical coherence tomography (EDI-OCT), uses spectral domain technology, and swept-source optical coherence tomography (SS-OCT) with faster

scanning engines and can image structures from the choroid to the inner sclera.[172] SS-OCT uses longer wavelengths compared with earlier generation OCTs, enabling improved penetration through the RPE and examination of deeper structures.[168,172]

EDI-OCT, as a result of a modification of the SD-OCT technique, enables the reliable imaging of the choroid in its full-thickness.[173,174] By permitting high-resolution visualization of the choroid, EDI-OCT is sensitive to recognizing thin lesions and possibly detecting a submillimeter early melanoma that might not be apparent with US.[175-177] Typical characteristics visible on EDI-OCT include deep optical shadowing, thinning or compaction of the choriocapillaris, disruption of the adjacent retinal photoreceptor layer, SRF with or without lipofuscin deposition, and intraretinal fluid.[177]

FAF is a non-invasive technique useful for identifying lipofuscin in pigmented choroidal lesions.[178-180] It is based on the stimulated emission of light from naturally occurring fluorophores, the most significant being lipofuscin.[180] A majority of naevi are not hyper-autofluorescent.[180] Naevi generally show a normal pattern of background FAF, but a minority of cases may reveal areas of a decreased FAF signal that is associated with chronic RPE degenerative features and atrophy.[180,181] Nearly 90% of CMs located at the posterior pole show at least one focus of increased autofluorescence.[182] SRF represents a barrier between the photoreceptors and the RPE, preventing their normal phagocytosis. As a result, they accumulate on the outer retinal surface and in the subretinal space and become a source of autofluorescence.[180]

Invasive methods, such as FAG and ICGA, which involve the injection of an intravenous dye, have been used to differentiate melanoma from a masquerading pathology to search for secondary neovascularization or ischaemia or to assist in visualizing lesions obscured by media opacities, but non-invasive methods have replaced these methods to a certain extent.[183,184] The imaging of the choroidal vasculature with ICGA may reveal microvascular patterns that can help to differentiate a naevus from a melanoma through the recognition of the typical features of melanomas, such as an irregularity of the lesion's margins; a heterogeneous, hyporeflective choriocapillaris plexus with avascular areas; hyperreflective choriocapillaris rings; thick choroidal vascular networks; and choroidal vascular loops.[169,185] The presence of haemorrhages and lipid exudation on ICGA as well as FAG are useful for the differential diagnosis of a malignant CM and choroidal metastasis as opposed to peripheral exudative haemorrhagic chorioretinopathy.[186] Typical findings of CM on FAG include hypofluorescence with mottled hyperfluorescence in the arterial or early venous phase. However, a small CM with an intact overlying RPE can demonstrate no appreciable abnormalities.[187-189] FAG can reveal OP clumps on the surface of the tumour, where these clumps appear to be hypofluorescent. SRF can be seen by the accumulation of fluorescein in the late frames, leading to hyperfluorescence.[187-189]

6.2.4. Observation for growth

Diagnosing a small CM may include observation with watchful waiting in the event that the diagnosis is not otherwise ensured.[1-3] Observation is thought to be justified and unable to impact prognosis[39] because it has been estimated that development of micrometastases initiates several years before the diagnosis of a CM.[190-192] However, it is not known when the dissemination takes place, but tumours as small as 3 mm in LBD and 1.5 mm in thickness have been predicted to be capable of dissemination.[193] Initial observation for growth might be appropriate in a majority of choroidal tumours less than 2.25 mm in thickness and in patients under 60 years of age since a majority of those tumors will belong to GEP class 1 (see below: 6.3.3: Cytogenetic prognosticators) and have a lower risk of metastases.[149]

Not all enlargement, however, represents true transformation into melanoma. Slow enlargement over years at a median growth rate of 0.06 mm/year has been shown to likely represent a benign naevus without transformation over time.[43,194] It is current practice to consider an enlargement over 0.5 mm within 2 years to be suggestive of a malignant tumour.[195]

De novo tumours become visible after 20 cell divisions still being less than 1 mm in size.[193] The development of a new naevus in adulthood or asymmetric growth is generally cause for suspicion and should be considered as a *de novo* melanoma until proven otherwise.[196-198]

6.2.5. Biopsy

Small lesions without sufficient clinical evidence for malignancy are either observed for growth and, particularly, growth rates or, if sufficiently conspicuous, are biopsied before being defined and treated as melanomas.[199,200] The biopsies today are performed more frequently for prognostic rather than diagnostic purposes.[201-205] Routine use of cyto- or histologic confirmation for diagnosis is not a current practice, unlike in a majority of other cancers, because of an over 95% accuracy rate of non-invasive diagnosis, at least for tumours thicker than 3.0–4.0 mm,[17,108,161,206,207] whereas, as high as one-third of small CMs are initially misdiagnosed clinically.[208] Despite the claimed risk for tumour dissemination secondary to diagnostic invasive approaches,[200] a biopsy has been shown to be sufficiently safe and successful for tumours as thin as 0.7–1.0 mm[209-211] and 2–3 mm[149,209,212-215] in LBD.

However, a fine-needle aspiration or vitreous cutter biopsy does not exclude the possibility of a malignant tumour, including with a non-malignant result, because the sample might not be representative of the entire tumour, particularly of those that are transformed naevi.[208,216,217] Conversely, a prognostic biopsy may occasionally return a wrong result.[218,219]

6.3. PROGNOSIS AND PROGNOSTIC FACTORS

6.3.1. General aspects of prognosis

In the TNM classification, the anatomical extent of the primary tumour is marked with a T category. Its regional lymph node involvement, which is extremely rare with UMs,[220-222] is represented under the N, and eventual metastases with the M. Patients with evident regional lymph node or systemic metastases, irrespective of the tumour size, are staged as a stage IV. Ten-year Kaplan-Meier survival estimates for small CMs without ciliary body involvement or an extraocular extension (T1, stage I) range between 88–94% (95% CI, 84–96%) and around 80% (95% CI, 75–84%) for medium sized (T2, stage IIA) CMs.[24,223]

Table 2. Current TNM stages of choroidal and ciliary body melanomas according to American Joint Committee on Cancer (AJCC)

Stage I	T1a	N0	M0
Stage IIA	T1b-d	N0	M0
	T2a	N0	M0
Stage IIB	T2b	N0	M0
	T3a	N0	M0
Stage IIIA	T2c-d	N0	M0
	T3b-c	N0	M0
	T4a	N0	M0
Stage IIIB	T3d	N0	M0
	T4b-c	N0	M0
Stage IIIC	T4d-e	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any N	M1a-c

6.3.2. Histopathological prognosticators

Three main cell categories are microscopically distinguished in UM: spindle cell, epithelioid cell, and mixed.[224] Spindle cell melanomas are associated with a better prognosis, mixed cell melanomas are associated with an intermediate prognosis, while epithelioid tumours grow faster, are more likely to metastasize, and are correlated with a shorter survival time.[140,225-229] The 15-year mortality rates of patients with spindle, mixed, or epithelioid cell melanoma are 19–26%, 59–60%, and 72–75%, respectively.[230,231] An increase in the number of mitoses per 40 HPF, a high fraction of PC-10 and Ki-67 indicating high cellular activity, a large mean diameter of the 10 largest nucleoli,[232-234] a high microvascular density,[232,235] an increased infiltration by lymphocytes[236] and macrophages[237,238], high expression of insulin-like growth factor-1 receptor,[239] a high expression of human leukocyte antigen I and II[240], and the presence of extravascular matrix network patterns loops and networks[241-243] have been associated with a worse prognosis.[224,225,242,244-247]

6.3.3. Cytogenetic prognosticators

The better prognosis of patients with small CMs compared to those with large CMs is likely related to fewer and less risky cytogenetic abnormalities of small CMs compared to larger tumors and, hence, a lower metastatic capacity.[4,103] UM carries distinctive molecular pathway defects, with its own chromosomal and molecular alterations.[248-250] Prognostic biopsies of conservatively treated UMs that allow for the analysis of their cytogenetic, gene expression, and molecular genetic features are not yet a routine part of the treatment of all UM patients, but are increasingly more common.

A complete or partial loss of chromosome 3, which occurs in approximately 50% of UMs, is associated with a reduction of 50% in survival.[251-256] This loss of chromosome 3 is generally associated with a multiplication of chromosome 8, 8q, or parts of 8q, and additional copies of chromosome 8q are correlated with a high mortality rate.[251,252] Monosomy 3 together with gains in chromosome 8q is thus associated with the highest risk for metastasis, whereas either monosomy 3 or gains in chromosome 8q are associated with an intermediate risk and disomy 3 with the lowest risk.[214,252,257,258] Chromosome 1 and chromosome 6 changes are frequent as well.[259-261] Loss of chromosome 1p correlates with a reduced survival rate,[262,263] whereas a chromosome 6p gain is suggestive of a protective effect and associated with a better prognosis.[264] The determination of the chromosomal status may be affected by prior irradiation.[265]

Several somatic mutations have been identified as having an influence on an UM patient's prognosis. Tumorigenesis is driven by mutually exclusive gain-of-function mutations in members of the Gq signalling pathway (GNAQ, GNA11, PLCB4, or CYSLTR2) followed by near-mutually exclusive mutations in BAP1, EIF1AX, SF3B1, or SRSF2.[266-268]

GNAQ and GNA11 mutations, members of the q class of the G-protein α-subunits, are found in all stages of UM, but additionally found in naevi.[85,88] Three times as many metastatic UMs carry mutations in GNA11 as compared to GNAQ, suggesting that cells carrying a GNA11 mutation are designated for the metastatic process.[83,84,269,270] Furthermore, PLCB4 and CYSLTR2 oncogenes are, similarly, a gain-of-function mutations leading to an activation of the same signalling pathway and thus promoting UM tumorigenesis.[271,272]

BAP1 has been mapped on a tumour suppressor gene located on chromosome 3, and its loss is a strong indicator for worse prognosis.[82,115,269,273] Whole-exome sequencing of metastatic UMs has identified inactivating somatic mutations in BAP1 in 84% of metastasizing tumours, suggesting that the inactivation of BAP1 is a pivotal event in the development of metastases.[82] Mutations of the X-linked translation initiation factor EIF1AX have a protective effect and are associated with an 8-fold decreased risk of metastasis.[87,269] Similarly, mutations in the splicing factor SF3B1 are correlated with improved survival

rates as well,[86,87,274] although there have additionally been studies that have concluded the opposite argument for this association.[87,269]

GEP is a technique which uses the mRNA of tumour biopsies in order to predict metastatic risk.[254,275] Based on the results of their GEPs, UMs are divided into two major prognostic subgroups: those in the class 1 with a low (class 1A) or intermediate metastatic risk (class 1B) and those in class 2 with a high risk.[114,203,254,276] Class 1 tumours are associated with disomy 3, and the gain of 6p, and class 2 tumours are associated with monosomy 3 and mutations in the BAP1.[82-85,88,114,271,272] Metastatic rates have been reported to be as low as 1% in class 1 and up to 26% in class 2 cases at a median follow-up time of 17 months.[203] Patients with a class 2 UM tend to be older, have thicker tumours with epithelioid cells as well as a high mitotic rates, and present BAP1 mutations.[203] Although the majority of metastases occur in patients with class 2 tumours, class 1 tumours may give rise to metastasis as well.[203] Preferentially expressed antigen in melanoma (PRAME) is an independent prognostic biomarker in UM that identifies increased metastatic risk in patients with class 1 or disomy 3 tumours.[277]

6.4. TREATMENT

6.4.1. Choice of primary treatment

A majority of CMs are conservatively managed with radiotherapy, although selected large tumours continue to be treated with enucleation[8,278,279] and certain tumours undergo local resection[280,281]. Conservative treatment of CM aims to destroy the tumour while preserving as much useful vision as possible.

Three major radiotherapeutic techniques are available: brachytherapy with various isotopes and radioactive plaques, external beam radiotherapy with photons from linear accelerators or gamma knives, and charged particle beams.[282-289] All of these tehniques are effective for CMs of all sizes and have high rates of local control with survival rates that are similar to those observed after enucleation.[72,290,291] TTT can be a safe method for selected patients with thin and small tumours,[52,53] but high recurrence rates with thicker tumours have been a concern.[53,292]

6.4.2. Ruthenium^{106} brachytherapy

6.4.2.1. Radiation with ruthenium^{106}

Treatment with a beta emitter Ru^{106} applicator was first introduced in 1964 in former East Germany.[45,293,294] It gradually became more popular, particularly within Europe in the 1970s to 1980s.[295-302] Ruthenium^{106}, with a half-life of 373.59 days, is suitable for CMs of up to 5.4 mm in thickness because the beta radiation has a limited depth of penetration.[9,303] The advantage of Ru^{106} over gamma emitters and proton beam when treating small CMs is

thought to be fewer radiation-related complications and thus better preservation of vision since it causes less damage to healthy tissue.[287,304,305]

6.4.2.2. Radioactive applicators

Round episcleral plaques are bowl-shaped and 10–25 mm in diameter (Fig. 2).[9] Notched plaques are available for juxtapapillary tumours and ciliary body tumours. Ruthenium[106] plaques are commercially manufactured as pure silver plaques with encapsulated radioactive Ru^{106}. Their outer surface is lined by a thick silver layer that absorbs more than 99% of the radiation to prevent irradiation of tissues surrounding the eye,[306] whereas the silver layer of the active inner side has a thickness of 0.1 mm. Eyelets allow the plaque to be sutured to the sclera. The activity of the Ru^{106} plaque depends on the size and shape of the plaque and ranges between 4.1–40.3 MBq, equal to 0.11–1.09mCi.[9]

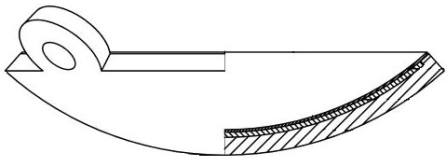

Figure 2. Round radiation plaque [9]

The radiation dose is delivered to the tumour during a precalculated and continuous time period. The planned dose and treatment period are directly proportional to the tumour thickness. The prescription point is determined by the tumour thickness, to which 1 mm is added for the sclera. The difference between the doses delivered to the sclera and apex increases with increasing tumour height. The prescription dose to the apex is generally 80–120 Gy, and frequently aims to deliver at least 250 Gy to the sclera[307], although certain centres prefer a scleral dose of 350Gy.[308] Scleral doses as high as 1,500 Gy using Ru^{106} have been administered without scleral necrosis,[309] which, however, remains a possible complication with such high doses.

The conventional practice is to position the plaque centred over the tumour to ensure that it overlaps the tumour margins by at least 2 mm in all directions.[6,282] The notion of scattered irradiation has induced certain centres to use eccentric plaque placement, with the posterior edge of the plaque aligned with the posterior tumour margin and without a safety margin in an attempt to save the fovea and optic nerve.[307,308,310] A wide radiation safety margin inevitably increases side-effects, particularly when the posterior tumour margin extends close to the optic disc or fovea.

6.4.2.3. Surgical technique

Total or partial peritomy is performed to expose the underlying sclera, followed by a disinsertion of the muscles if the muscles are located in the tumour area in order to enable plaque positioning over the sclera. The tumour margins are identified, for example, by transilluminations or indirect ophthalmoscopy with indentation and are marked with diathermy or ink. For plaque positioning, a non-irradiating dummy plaque is used. Once it is placed correctly over the tumour, it is replaced with the radioactive plaque. Intra- and post-operative US can be useful to confirm the exact plaque positioning.[311,312] A mattrass

suture over the plaque is recommended but is impossible when treating posterior tumours with the smallest plaques. The plaque cannot be placed closer than approximately 1.5 mm from the margin of the optic disc because of the optic nerve sheath, which has a diameter of 5.1 mm behind the eye.[313] When the radioactive plaque is fixed to the sclera, any disinserted rectus muscles are resutured over the plaque, and the conjunctiva is closed. When the prescribed radiation dose has been delivered, the plaque is removed during a second procedure. Any disinserted rectus muscles are replaced in their anatomical position. The inferior oblique muscle is generally left unattached since it has frequently been only partially disinserted.

6.4.2.4. Local tumour recurrence

Ru^{106} brachytherapy provides 5-year local recurrence rates from 2–15% for small and medium sized CMs when not restricted to a particular plaque size.[303,307,314-317] A larger tumour size and posterior location are risk factors for recurrence.[303,318] Although a majority of recurrences occur within the first few post-operative years, regrowth, including after 15 years, has been reported.[309] An increase in tumour size after initial tumour regression may occasionally further result from an intratumoural haemorrhage and does not necessarily indicate a local recurrence.[319]

6.4.2.5. Ocular side-effects of radiotherapy

CMs are resistant to radiation, and their treatment, therefore, requires high radiation doses that may result in radiation-related complications and impaired best corrected visual acuity (BCVA). Brachytherapy of small posterior CMs with Ru^{106} leads to posterior segment complications such as radiation maculopathy, retinopathy and optic neuropathy, as well as vitreous haemorrhage, whereas anterior segment complications such as cataract and iris neovascularization, with or without neovascular glaucoma, are rare.[308,309,317,320-323]

Radiation maculopathy appears clinically as retinal vascular changes such as microaneurysms, telangiectasias, retinal haemorrhages, microinfarcts, macular oedema, neovascularization, and lipid exudation.[31,324,325] Diabetic patients are at a higher risk.[326] Bevacizumab and intravitreal or periocular triamcinolone can transiently reduce macular oedema to maintain visual acuity (VA).[311,327] Maculopathy caused by exudates and oedema can be treated by administering TTT to the tumour if the tumor is located outside the macula. The 5-year cumulative incidence rate of developing radiation maculopathy following Ru^{106} brachytherapy is 30–55%.[302,308,310,328]

Radiation optic neuropathy is a less common complication after treatment of small posterior tumours with Ru^{106}, presenting in up to 12% of cases after 5 years.[302] This risk is related to the distance of the posterior tumour margin to the optic disc and is minimal beyond 4 mm.[328,329]

6.4.2.6. Vision outcome

Radiation retinopathy and maculopathy continue to be vision-limiting complications following radiation exposure.[330] Ru^{106} brachytherapy may allow to for the retaining of useful vision for a considerable period of time.[300] Risk factors for losing vision after brachytherapy are older age, a lower initial BCVA, a tumour location close to the fovea or optic disc, a larger tumour thickness, and a temporal tumour location.[307,309] Three to 5 years after brachytherapy, approximately 50% of patients maintain a BCVA of 20/200 (decimal scale, 0.1) or better, and 30% a BCVA of 20/50 (decimal scale, 0.4) or better in the tumour eye.[309,331] When using eccentric placement, up to 75 % of patients with their posterior tumour edge at least 3 mm from the fovea may retain 20/40 (decimal scale, 0.5) BCVA at 4 years after brachytherapy.[308,310] Vision can further improve after radiation due to a resolution of SRF following tumour regression.[57-59,332,333]

When compared with Pd^{103}, Ru^{106} brachytherapy is associated with improved preservation of vision.[287] Following I^{125} brachytherapy, a good local tumour control of approximately 90% at 10-years has been achieved for small CMs, but the risk for a BCVA loss of 3 Snellen lines or more or deterioration of BCVA to less than 20/200 (decimal scale, 0.1) is approximately 50% at 10 years.[334] With proton beam radiation therapy, a nearly 100% local tumour control and satisfying long-term visual outcomes for tumours located further than 3 mm from the fovea and optic disc have been achieved after treatment of small tumours.[335,336] The probability of patients retaining BCVA of 20/200 or better was approximately 50% at 10 years.[335]

6.4.3. Transpupillary thermotherapy

TTT was introduced in the Netherlands as a treatment modality for CMs in 1995.[48,337,338] It was initially described in combination with Ru^{106} brachytherapy in an attempt to avoid radiation-related complications and preserve BCVA by reducing the radiation dose.[48-50,339] However, the reduction in loss of BCVA proved to be insignificant compared to treatment with Ru^{106} alone.[314,340] TTT is now additionally used as a primary therapy or adjuvant therapy after brachytherapy.[307]

In TTT, a diode laser beam is directed through the dilated pupil to the apex of the tumour for approximately one minute, resulting in an increase in the tumour temperature to 45-60°C. The consequence of this heating is a tumour necrosis to a maximum depth of 4 mm,[337,338] which is therefore considered to be the size limit for the indication of TTT as a primary treatment.[48,57,338,341-343] Tumour regression continues for months and leaves an atrophic chorioretinal scar. The importance of aiming for a completely flat tumour scar is to reduce the risk of a local recurrence, although recurrent tumours have been reported to arise from completely flat scars.[55,56,333,344]

When a tumour is small and thin, TTT may be considered as a primary treatment provided that the patient accepts that such treatment may need to be followed by radiotherapy in cases of recurrent or persistent tumours.[53] TTT causes an immediate local scotoma in the visual field, and delayed effects include macular scarring, epiretinal membranes, retinal vascular occlusions, and vitreous haemorrhages.[292,342,344]

High local recurrence rates, up to 45%[52-60] have been a concern following TTT. Several studies have reported higher recurrence rates for parapapillary tumours compared to non-parapapillary lesions.[57,59,337,342,345] The overlying retina undergoes atrophy, but the underlying sclera is resistant to hyperthermia.[338] Consequently, TTT may be associated with intra- and extra-scleral recurrences, which are rare after brachytherapy.[52,53]

6.4.4. Proton beam therapy

One option for radiotherapy is external beam radiation using charged particles such as protons[283] despite facilities for proton beam only being available in a limited number of centres around the world. This technique allows for a uniform dose distribution to a circumscribed target volume including the tumour, resulting in improved local tumour control and less damage to healthy tissues.[346] Proton beam therapy is generally preferred for larger tumours that are not eligible for brachytherapy or for posteriorly located tumours, in an attempt to spare the macula and optic disc.[347]

Local tumour recurrence rates for CM of patients with tumours of all sizes have been reported at approximately 4% at 5 years[347] and 5% at 10 years.[348] The local recurrence rate was 5% at 15 years for tumours with a median of 5.3 mm in thickness and 13.2 mm in LBD.[349] For T1 tumours, no recurrences were observed during a mean follow-up of 10 years.[335]

BCVA outcomes following proton beam therapy depend on tumour thickness and proximity to the fovea and optic disc.[335,350] Patients with a tumour located at least 3 mm from these posterior structures generally do not develop clinically significant radiation vasculopathy.[351] The risk for visual loss at 5 years has been estimated at 68% for small and medium-sized tumours.[352] Five-year cumulative rates of maculopathy and papillopathy were 64% and 35 % when the analysis was restricted to a group of patients with small- to moderate-sized tumours located within 4 disc diameters of the optic nerve or macula.[352] The frequency of losing BCVA of 20/200 for tumours located further than 3 mm from fovea and optic disc was approximately 7% at 5 years, and 18% at 10 years.[335] The corresponding rates for tumours located closer than 3 mm from the posterior structures was approximately 40%% at 5 years and 53% at 10 years.

6.5.5. Experimental treatments

Photodynamic therapy (PDT) with verteporfin was originally used for choroidal neovascularization in age-related macular degeneration.[353] It has been reported that PDT induces tumour regression for 62% to 100% of treated small posterior CMs,[354,355] resulting in treatment outcomes that are less reliable with regard to tumour regression compared to other treatment modalities[356] but without the associated decrease in BCVA.[355,357] Although PDT has been reported to be effective in both amelanotic and pigmented tumours,[358] doubts have been raised concerning its efficacy in treating the pigmented tumours.[359,360] PDT was additionally reported to be more effective for treating tumours with three or fewer risk features for growth.[354]

AU-011 is a novel virus-like particle-drug conjugate that selectively binds to cancer cells and enables a targeted therapy for UM.[361,362] The drug is administered through intravitreal injection and subsequently activated with an infrared laser, which leads to targeted tumour cell necrosis while simultaneously sparing healthy tissue.[363] Preliminary results support the further development of this modality.[364]

6.6. METASTASIS AND SURVIVAL

Metastatic UM is the leading cause of death in UM patients, with the mortality rate being higher than 50% after 25 years of primary treatment for medium-sized and large tumours.[20,92,365,366] Small tumours have a much better prognosis, with a metastatic rate of approximately 12% in 10 years.[24] It is not known exactly when dissemination takes place. Clinically evident metastases are detected in less than 1–3 % of all patients at the time of UM diagnosis, and the median length of time until detection of metastasis is 2 years after treatment for UM in general.[92,367] It has been estimated that tumours may have the capacity to disseminate years before the diagnosis of the primary tumour.[190,368] Studies of tumour doubling times of metastatic lesions have suggested that metastasis may commence when the primary tumour continues to be small, that is approximately 3 mm in LBD and 1.5 mm in thickness.[193] The smallest CMs that have been reported to metastasize have been at least 1.7 mm thick[369] and 5.0 mm in LBD[156,292,369-375]. Growth of metastases may be delayed, and metastases may appear clinically up to three decades after successful treatment of the primary tumour due to a slow growth pattern and later cytogenetic progression.[20,92,190]

UM has a predilection to metastasize to the liver in over 90% of cases.[19,376,377] Liver is the only site in 33–56% of metastatic patients.[5,92,366,376,378] Other less common, and generally secondary, sites are the lungs, subcutaneous tissue, bones, brain, adrenal glands, and the heart.[19,376,379-381] Metastases are more widespread than clinically suspected in patients who undergo autopsy.[366] Symptoms vary, depending on the affected organ; yet, more than 60% of patients are asymptomatic when their metastases are detected.[382]

When a six-monthly screening protocol is applied, metastases are detected before the onset of symptoms in more than 90% of UM patients.[383] Different protocols have been reported, but a majority of UM patients are checked for liver metastases every 6 or 12 months, depending on their tumour stage, using imaging techniques such as abdominal US, MRI, and liver function tests (LFTs).[382-385] New abnormalities in the LFTs or appearance of the liver are highly suggestive of metastasis. However, LFTs can be normal in approximately one-third of cases with liver metastasis.[382] Abdominal US combined with LFTs is a sensitive screening modality, particularly when followed by a confirmatory MRI in cases of newly detected lesions.[386] A histopathological confirmation of suspected metastases is performed if possible – and certainly when active treatmen is to be proposed – depending on the general condition of the patient.

In the presence of metastases, survival prognosis is poor as no curative treatment is generally available at the moment. The median survival of patients with metastatic UM ranges from 6 to 13 months.[23,367,387,388] The death rate following clinically diagnosed dissemination is 80% at 1 year and 92% at 2 years, and a long-term survival time of more than 5 years is exceptional.[19,389-391] Systemic treatment can only slow metastatic growth and improve survival to a limited extent.[5,388]

Although there are many therapeutic options, there is no established standard of care for patients with metastatic disease. These options include systemic and intrahepatic chemotherapy, transarterial chemoembolization, isolated hepatic perfusion, protein kinase inhibitors, selective internal radiation therapy, immunoembolization, immunosuppressants, partial hepatectomy, microwave ablation, selective internal radiotherapy, and liver-directed thermotherapy.[23,389] With a local resection of solitary liver metastases, a survival of seven years has been reported, but this is only available for a minimal number of selected patients.[392-395] Patients with a loss-of-function mutation in the MBD4 gene are likely to benefit from CPI immunotherapy, a group of agents successfully used in cutaneous melanoma therapy.[118,130-132]

7. Aims of the study

The first two studies (Study I and II) in this thesis analysed the treatment results of small CMs of less than 10 mm in LBD with the 10-mm Ru^{106} plaque. The second study compared these results with those of similarly sized melanomas treated with the 15-mm Ru^{106} plaques. The third study (Study III) reported sizes and clinical features of the smallest CMs that metastasized. The fourth study (Study IV) reported the growth rates and doubling times of presumed incipient CMs.

The specific aims of this study were as follows:

I. To assess local tumour control, side-effects, and BCVA in a population-based consecutive series of patients who received brachytherapy for CM less than 10 mm in LBD with the 10-mm Ru^{106} plaque.

II. To assess local tumour control, side-effects, and BCVA in a population-based consecutive series of patients who received brachytherapy for CM less than 10 mm in LBD with the 10-mm or 15-mm Ru^{106} plaque and compare the outcomes between two groups.

III. To empirically determine the size limit at which a small CM acquires the capacity to metastasize and to assess the clinical characteristics of small fatal CMs

IV. To analyse tumour doubling times and growth rates as potential alternative diagnostic criteria for incipient small CMs in a population-based study with a consecutive series of patients with presumed incipient CM that was subsequently managed with primary TTT

8. Material and methods

8.1. PATIENTS AND STUDY DESIGN

8.1.1. Studies I and II

Patients who were clinically diagnosed with a CM less than 10 mm in LBD and managed with primary brachytherapy with the 10-mm (Study I and II) or a 15-mm (Study II) Ru^{106} plaque were eligible to participate in these studies. A patient was ineligible if the tumour involved the ciliary body or iris. The database of the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, a national referral centre for UM patients, was reviewed.

The time period for Study I began in October 1998 – at which point the 10-mm plaque became a treatment of choice in Helsinki University Hospital – and ended in December 2010, with follow-up data being collected until the end of 2011. Within this time period, a total of 118 patients with an UM less than 10 mm in LBD were identified, of whom, 48 were treated with the 10-mm plaque. Three patients had a ciliary body or iris tumour, resulting in 45 patients being enrolled.

The time period of Study II began in October 1998 as well. Patients were treated with the 10-mm or 15-mm plaque until December 2014, and follow-up data were collected until the end of 2017. Within this period, a total of 234 patients with CMs less than 10 mm in LBD were identified, of whom, 76 were scheduled for treatment with the 10-mm and 88 were scheduled with the 15-mm plaque.

8.1.2. Study III

Data on consecutive patients diagnosed with a CM of 3 mm or less in thickness and 9 mm or less in LBD who subsequently developed metastases were collected from 10 ophthalmic oncology centres in Europe that agreed to participate in the study, including 9 patients from the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital. The data of 56 patients were collected, of whom, 11 were excluded after an eligibility check and 45 enrolled. Excluded were 5 patients who had tumours larger than the eligibility criteria, 3 patients who had incomplete key data, one patient who was diagnosed with pulmonary metastases from an epithelioid cell melanoma, and 2 patients who had only extrahepatic metastases without histopathological verification. The patientes had been were diagnosed with CM between 1962 and 2010.

8.1.3. Study IV

All 9 consecutive patients who had been diagnosed with a presumed incipient CM following documented growth and subsequently treated with primary TTT between 2010 and 2017 in

the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital were eligible for this retrospective study. One of the patients had a previous T2aN0M0, Stage IIA, CM in the same eye that had been treated with the 15-mm ruthenium plaque 2.5 years before the second tumour (enrolled in the present study) was diagnosed.

8.2. PRIMARY TREATMENT

8.2.1. Brachytherapy (Studies I and II)

The treatments were performed by three experienced ocular oncologists over the 16-year period. The prescription point was tumour thickness plus 1 mm for the sclera. Treatment times and doses were calculated from the central axis depth dose curve. The standard prescription dose was either 100 Gy or 120 Gy to the apex depending on the thickness of the tumour and aimed to deliver a minimum dose of 250 Gy to the sclera. Overlying extraocular muscles were disinserted if needed to ensure accurate positioning of the plaque in relation to the tumour.

The cord diameter of the radiation window of the plaque in spherical form is 9.4 mm and 12.9 for 10-mm and 15-mm plaques, respectively (Eckert & Ziegler BEBIG GmbH, Berlin, Germany). The radiation window is surrounded by a 0.75-mm-wide inactive border. The radiation window is surrounded by a penumbra of scatter radiation, which is used as justification for eccentric plaque placement in order to limit irradiation to adjacent tissues.[310,396] Plaque position and distance to the tumour apex were verified on the first postoperative day with US in view of a calculation update of the treatment time. However, this practice was not in use in the early study years.

8.2.2. Transpupillary thermotherapy (Study IV)

TTT was delivered through a dilated pupil in periocular anaesthesia with an infrared diode laser (MedArt 426, MedArt, Hvidovre, Denmark) at a wavelength of 810 nm which was adapted to a slit lamp biomicroscope and which used beam diameters of 0.8 to 3.0 mm and a contact lens (Area Centralis or Quadraspheric, Volk Optical, Mentor, OH). The spot was applied 1 to 4 times with increasing power if needed (median, 1,500 mW; range, 700–3500) for a median duration of 120 s (60–285) to achieve a greyish white colour on the surface of the tumour. Overlapping spots, if needed, were used to cover the entire tumour, and there was a margin of 0.5 to 1.0 mm on all sides. TTT was repeated 1 to 5 times at intervals of 2–7 months with a goal of achieving a white chorioretinal scar. Three ocular oncologists performed all treatments.

8.3. DATA COLLECTION

8.3.1. Clinical evaluation

8.3.1.1. Studies I and II

The tumour size was primarily determined by indirect ophthalmoscopy and B-scan US. Biomicroscopy and indirect ophthalmoscopy were used to localize the tumour margins in order to measure the distance from the posterior tumour margin to the optic disc and foveola and evaluate the presence of SRF and OP. Patients were treated if they had a presumed small CM that either had been observed to grow or had high-risk features for growth[27,42,397] (Tables 3–4). The BCVA was measured using a test-type projector (Rodavist 2 and 524; Rodenstock GmbH, Ottobrunn, Germany) in even decimal steps from 20/20 (decimal scale, 1.0) to 20/200 (decimal scale, 0.1) plus 20/400 (decimal scale, 0.05). A BCVA worse than 20/400 was recorded as counting fingers at 2 m, 1 m, and 0.5 m; hand movement; light perception; and no light perception.

Table 3. Risk factors for growth[27,42] in 45 (Study I) and 164 (Study II) patients with small choroidal melanomas less than 10 mm in largest basal diameter, of whom 76 were managed with the 10-mm plaque and 88 with the 15-mm plaque (Studies I and II). Study I patients are included in Study II.

					Observed Growth, n (%)			
	Study I n (%)	Study II, n (%)			Study I n (%)	Study II, n (%)		
Risk Factors	10-mm n=45	10-mm n=76	15-mm n=88	*P**	10-mm n=18	10-mm n=29	15-mm n=32	*P**
Thickness >2 mm	18 (40)	30 (39)	63 (72)	<0.001	6 (33)	6 (21)	19 (59)	0.004
Subretinal fluid	28 (62)	48 (63)	55 (63)	0.99	5 (28)	8 (28)	11 (34)	0.81
Symptoms	25 (56)	40 (53)	39 (44)	0.35	5 (28)	8 (28)	5 (16)	0.35
Orange pigment	28 (62)	47 (62)	45 (51)	0.21	7 (39)	13 (45)	11 (34)	0.44
Margin								
touching disc	3 (7)	3 (4)	1 (1)	0.34	1 (6)	1 (1)	0 (0)	0.48
within 2 DD	26 (58)	40 (53)	41 (47)	0.53	5 (28)	8 (28)	14 (44)	0.19

DD = disc diameter, *Fisher's exact test

Table 4. Number of risk factors[42] for growth in 45 (Study I) and 164 (Study II) patients with small choroidal melanoma less than 10 mm in largest basal diameter who were treated with the 10-mm and the 15-mm ruthenium[106] plaque. Study I patients are included in Study II.

	Study I	Study II, n (%)		
	n (%)	----------		
Number of	10-mm	10-mm	15-mm	
Risk Factors	n=45	n=76	n=88	*P**
0	4 (9)	9 (12)	5 (6)	0.12
1	5 (11)	9 (12)	10 (11)	
2	9 (20)	16 (21)	17 (19)	
3	11 (24)	14 (18)	30 (34)	
4	11 (24)	19 (25)	21 (24)	
5	5 (11)	9 (12)	5 (6)	

*non-parametric test for trend

In Study I, 4 (9%) patients who had none of the risk features were treated due to observed growth. In Study II, 14 patients had a tumour without risk features, of whom, 12 (7%) were treated because of observed growth, one had a tumour that had not been seen during regular glaucoma follow-up, and one had a ruptured Bruch's membrane.

8.3.1.2. Study III

This retrospective study was conducted using patient charts, archival images, and pathology data. Members of the European Ophthalmic Oncology Group submitted anonymous data from 10 ocular oncology services to a secure survey website. The data requested included date of birth, diagnosis, primary treatment, local recurrence, and diagnosis of metastases as well as sex, ethnicity, involved eye, BCVA, history of a previous naevus, high-risk features for growth and metastasis,[27,42] observation before treatment, type of the primary treatment, histopathologic diagnosis, secondary treatments, systemic treatment, and last status.

8.3.1.3. Study IV

Digital fundus images were used to localize the tumour margins in order to estimate the distance from the posterior tumour margin to the optic disc and foveola and to evaluate its growth as well as the presence of SRF and OP. Based on OCT, a tumour was considered flat if the tumour area was not elevated compared to the adjacent normal choroid. The BCVA was measured using a test-type projector (Rodavist 2 and 524; Rodenstock GmbH, Ottobrunn, Germany) in even decimals from 1.0 (20/20) to 0.1 (20/200).

Diagnosis was based on verified tumour growth relative to the age of the patient and reported chance of having a growing choroidal nevus, TDT, growth rate, and to the calculated age of tumour origin. Patients were selected to have primary TTT instead of brachytherapy due to the small tumour sizes.

The initial data were collected from the medical records of each patient, including details on age, race, gender, diabetes, ocular history, tumour growth, high-risk factors, BCVA, tumour location, tumour measurements, and information from TTT. Data after completion of TTT included final BCVA, tumour control, TTT complications, and last status.

8.3.2. Calculations of growth rates and doubling times

For this study, the tumour growth rate was calculated starting from its LBD and using a theoretical measure of 0.05 mm when the tumour was not visible in the first photograph. The tumour volume was then estimated presuming a cylindrical form because all tumours were assumed to have the same thickness as the choroid since the tumours did not thicken the adjacent choroid on the OCT images. The surface area of the tumour was calculated by using ImageJ software (National Institute of Health, Maryland, USA, Version 1.51). Two investigators measured the tumour area independently by two different methods (manual drawing and automatic recognition of tumour margins) and the final area that was taken was the mean of these four measurements. The date of the diagnosis of the primary tumour was the day on which an ophthalmologist first made the diagnosis of CM due to verified growth. The date of first observation was the date when the lesion had been first documented. Observation time (T) was the difference between these two dates.

TDT was calculated according to Schwartz[398]:

$$TDT = \frac{T}{\left(\frac{\log 10\left(\frac{Vdg}{Vini}\right)}{\log 10(2)}\right)} \qquad \text{(equation 1)}$$

where T = observation time, Vdg = tumour volume at diagnosis, and Vini = initial tumour volume.

The predicted initial age was additionally calculated to estimate whether the tumours had originated in adulthood and thus, were likely to be *de novo* tumours (equation 2). A theoretical initial LBD of 0.05 mm was used when a tumour likely would have been visible.

$$Age_{pred} = Age_{ini} - \frac{TDT \times \frac{\log 10\left(\frac{Vini}{Vorig}\right)}{log 10(2)}}{365.25} \qquad \text{(equation 2)}$$

where Age_{pred} = age when the tumour was predicted to be visible, Age_{ini} = age when the tumour was initially observed, TDT = tumour doubling time (equation 1), Vini = initial tumour volume, and Vorig = theoretical volume 0.000125 mm^3 based on 0.05 mm diameter. Calculations were based on a presumed constant exponential growth.[399]

For comparison, TDTs collected for 196 patients with a UM reported in 4 articles to serve as reference data.[191,192,400,401] Omitting two outliers with exceptionally long TDT,[191] the median

UM TDT was 521 days (range, 10–8766). The reported median growth rate for choroidal naevi, that is 0.04 mm/year (range, 0.01–0.2) and 1.1 %/y (range, 0.2–11.6), for 89 naevi that showed photographic evidence of enlargement[43] – excluding a tumour that later had been diagnosed as a CM – was used as a counter reference.

8.3.3. Assessment of outcomes (Studies I and II)

Patients were followed at 3, 6, and 12 months; then every 6 months until 3 to 4 years after brachytherapy, and annually thereafter. Biomicroscopy, indirect ophthalmoscopy, fundus photography, and B-scan echography (I3 System-ABD; Innovative Imaging, Sacramento, California) were used to assess tumour control. Recurrences were coded as being vertical, marginal, diffuse, or extrascleral.[402]

The location of the plaque was retrospectively modelled in relation to the tumour to facilitate determining the reasons for a local recurrence. The location of the plaque was coded as 'covering the entire tumour with a safety margin' (covered), as 'being parallel' (eccentric), or as 'not covering the entire tumour' (not covered). A circle was digitally drawn to the post-treatment photographs, that corresponded in size to the radiation window. This was done using radiation and diathermy scars, with the presumption that the diameter of the optic disc was 1.5 mm.

Complications were assessed, as outlined, in a previous study on brachytherapy from the same ocular oncology service.[403] Radiation maculopathy was diagnosed based on the appearance of retinal haemorrhage, mircoaneurysms, microinfarcts, oedema, exudation, and a decrease in BCVA. A tumour recurrence involving the fovea, scarring, or a macular pucker were categorized as 'maculopathy for other reasons'. Optic neuropathy was categorized as radiation optic neuropathy based on the appearance of oedema, peripapillary splinter haemorrhages, or microinfarcts.

8.3.4. Assessment of survival and metastatic status (Studies I and II)

LFTs and upper abdominal US were performed at the time of diagnosis and annually thereafter, and a chest radiogram was performed only at diagnosis. Conspicuous findings of concern were verified with CT or MRI and, eventually, histopathologically. Causes of deaths were verified from death certificates obtained with permission from Statistics Finland, autopsy reports, and patient charts.

8.4. STATISTICAL METHODS AND DATA ANALYSIS

Follow-up data were collected prospectively into a dedicated database (MS Access; Microsoft, Seattle, WA) and analysed with Stata statistical software (Release 10, 13 and 15; Stata Co, College Station, TX). A cumulative incidence analysis[404] was used that accounted for competing events in order to analyse the time to individual complications and death

– except in the third study where the analysis of time to systemic metastasis and survival was based on the Kaplan-Meier product-limit method since, by definition, all patients developed systemic metastases and none died of other causes.

All tests were 2-tailed, and a P-value less than 0.05 was considered statistically significant. The data were summarized as frequencies and percentages for categorical variables and as a median with a range for continuous variables. A Fisher's exact test was used to compare dichotomous variables. A non-parametric test for trend was used exploring the differences between two independent groups for ordinal variables. A Kruskal-Wallis test was used between two or more independent groups for continuous variables, and a Gray's k-sample test[405] was used to compare cumulative incidences between two groups. Parameters including the time to local recurrence, low vision (BCVA < 20/65; decimal scale, 0.3), and blindness (BCVA < 20/400; decimal scale, 0.05) were modelled by univariable and multivariable Cox proportional hazards regression.

9. Results

9.1. TREATMENT WITH THE 10-MM OR 15-MM PLAQUE (STUDIES I AND II)

9.1.1. Baseline patient, eye, and tumour characteristics

All tumours treated with the 10-mm plaque were classified as T1aN0M0, stage I, by the AJCC TNM-System. Eighty-two percent of tumours treated with the 15-mm plaque were classified as T1aN0M0, stage I, and the remaining tumours with a thickness over 3 mm and LBD over 9 mm were classified as T2aN0M0, stage IIA (Fig. 3).[145]

The melanomas of the patients treated with the 15-mm plaque were thicker as a group (median, 1.9 vs 2.6 mm, *P*<0.001), had larger LBDs (median, 7.1 vs 8.6, *P*<0.001) and longer distances from the posterior tumour margin to the center of the fovea (median, 2.0 vs 2.8, *P*<0.001) (Table 5, Fig. 3). In Study II, the median age at diagnosis (65 vs. 63 years; *P*=0.59), the median follow-up time for patients who were still alive (8.1 years, range 3.0–18.8 vs. 8.9 years, range 1.1–17.9; *P*=0.67), and the median BCVA (20/25 vs. 20/30; P=0.54) were comparable between the two groups (Table 5).

Table 5. Baseline characteristics at the time of diagnosis of 45 (Study I) and 164 (Study II) patients with a small choroidal melanoma less than 10 mm in largest basal diameter irradiated with the 10-mm (Studies I and II) or the 15-mm (Study II) ruthenium[106] plaque. Study I patients are included in Study II.

	Study I median (range)	Study II, median (range)		
Characteristic	10-mm n=45	10-mm n=76	15-mm n=88	*P**
Age, years	61 (26–88)	65 (26–88)	63 (27–88)	0.59
Follow-up time, years	5.2 (0.3–11.9)	8.1 (3.0–18.8)	8.9 (1.1–17.9)	0.45
Thickness, mm	1.9 (0.4–5.2)	1.9 (0.4–5.2)	2.6 (0.3–5.7)	<0.001
LBD, mm 7.0 (3.3–9.6)	7.1 (3.3–9.6)	8.6 (4.1–9.9)	<0.001	
Distance to foveola, mm	2.0 (0–8.5)	2.0 (0–13.0)	2.8 (0–13.5)	<0.001
Distance to optic disc, mm	3.0 (0–7.5)	3.0 (0–13.5)	3.0 (0–13.5)	0.79
BCVA	20/25	20/25	20/30	0.54

BCVA = Best corrected visual acuity, LBD = Largest basal diameter, * Kruskal Wallis test

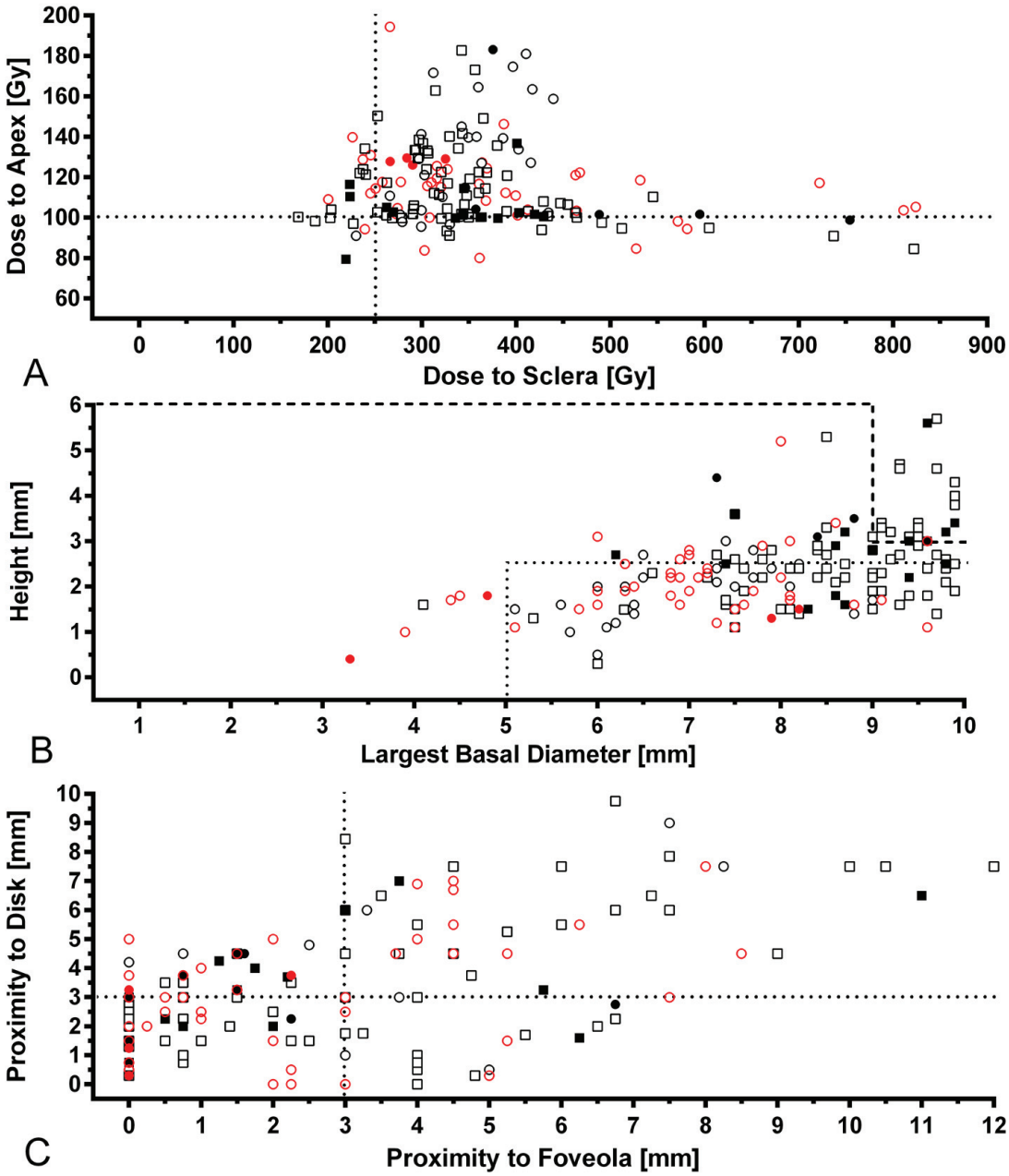

Figure 3. 45 (Study I, red symbols) and 164 (Study II) small choroidal melanomas less than 10 mm in largest basal diameter (LBD) irradiated with the 10-mm (circle, red and black) or the 15-mm (square black) ruthenium[106] plaques. A, Scatterplot of radiation dose to the sclera against dose to the tumour apex. Dashed lines indicate minimum prescription doses. B, Scatterplot of LBD against tumour height. Long and short dashed lines enclose tumours which fulfil the American Joint Committee for Cancer (AJCC) Tumour, Node, Metastasis (TNM, 8th Edition)[145] and the Collaborative Ocular Melanoma Study (COMS)[31] criteria for a small UM, respectively. C, Scatterplot of proximity of tumour margin to the foveola against proximity to the optic disc. Dashed lines indicate a distance of 2 DD (3 mm) from these structures, frequently considered to be a safety margin for not developing radiation maculopathy and optic neuropathy from ruthenium[106] brachytherapy. A–C, Solid and open symbols indicate tumours with and without recurrence, respectively.

9.1.2. Plaque positioning

The location of the plaque was assessed according to the surgical charts and by retrospective modelling (Table 6). In the comparative Study II, tumour coverage was statistically significantly different between the two groups (P=0.002) but differed to a lesser extent (*P*=0.052) after remodeling.

Table 6. Location of the plaque according to the surgical charts and by retrospective modelling of 45 (Study I) and 164 (Study II) patients with a small choroidal melanoma less than 10 mm in largest basal diameter irradiated with the 10-mm (Studies I and II) or the 15-mm (Study II) ruthenium[106] plaque.

	Surgical chart, n (%)				Modelling, n (%)			
	Study I	Study II			Study I	Study II		
Location	10-mm	10-mm	15-mm	P*	10-mm	10-mm	15-mm	P*
Covered	13 (29)	25 (33)	50 (57)	0.002	6 (13)	33 (43)	35 (40)	0.052
Eccentric	20 (44)	28 (37)	28 (32)		13 (29)	13 (17)	29 (33)	
Not covered	10(22)	22 (29)	10 (11)		18 (40)	24 (32)	16 (18)	
Indeterminate	2 (4)	1 (1)	0		7 (16)	6 (8)	7 (8)	

*non-parametric test for trend

9.1.3. Local tumour recurrence and survival

A total of 4 patients developed a local recurrence in Study I. A local recurrence was detected in 9 and 16 patients treated with the 10-mm and the 15-mm plaque, respectively, in Study II. Recurrences were controlled with a secondary iodine plaque, except in three patients, of whom one had been retreated with a secondary Ru[106] plaque and two had been treated with TTT. In Study II, the cumulative incidence of developing a local recurrence was comparable between the two groups (Table 7). By univariable Cox regression, a local recurrence was associated with an eccentric plaque location (HR 3.40 for a plaque not covering the tumour with a safety margin, *P*=0.024) (Table 6, Study II).

Of the 45 patients in Study I, 6 died during the follow-up. Five patients died for reasons other than metastatic disease, and one death was classified as being the result of possible metastasis to the brain as the only site, although this had not been histopathologically verified. Within the Study II period, a further 3 patients died of metastatic CM after a local tumour recurrence following treatment with the 10-mm plaque. Seven patients, of whom 4 had experienced a local tumour recurrence, died of metastatic CM after treatment with the 15-mm plaque. The development of metastases, all-cause, and melanoma-related mortality rates were comparable (Table 7). The time from treatment to metastases (median, 4.6 vs 4.5

years; *P*=0.85) and survival after diagnosis of metastases (median, 3.6 vs 6.1 years; *P*=0.73) were comparable between the two groups.

Table 7. Summary of outcomes using cumulative incidences after treatment of 164 patients with small choroidal melanomas less than 10 mm in largest basal diameter with the 10-mm or the 15-mm ruthenium[106] plaque

	Percentage at 5 years, (95% CI)			Percentage at 10 years, (95% CI)		
	Study I	Study II				
Outcome	10-mm	10-mm	15-mm	10-mm	15-mm	*P**
Recurrence	9 (3–20)	9 (4–17)	13 (7–20)	13 (6–21)	15 (8–23)	0.31
Metastases		4 (1–10)	6 (2–13)	4 (1–10)	10 (4–19)	0.50
All-cause mortality	11 (4–26)	10 (4–18)	9 (4–17)	24 (13–37)	29 (19–40)	0.24
Melanoma-mortality		3 (1–8)	2 (0.5–7)	3 (1–8)	8 (3–15)	0.33
Maculopathy						
Radiation	28 (15–42)	19 (11–28)	18 (11–27)	24 (15–35)	22 (14–32)	0.99
Other	15 (6–27)	4 (1–11)	1 (0.1–6)	10 (4–21)	10 (4–19)	0.54
Optic neuropathy	3 (0–12)	1 (0.1–7)	8 (3–15)	1 (0.1–7)	8 (3–15)	0.054
Low vision	17 (7–31)	14 (7–24)	24 (15–34)	21 (11–33)	30 (20–41)	0.36
Blindness	3 (2–12)	3 (0.6–10)	6 (2–13)	14 (6–25)	13 (6–23)	0.90

CI = Confidence interval, *Gray's k-sample test

9.1.4. Radiation maculopathy and optic neuropathy

Radiation maculopathy and optic neuropathy were the most frequent radiation- related complications. Radiation maculopathy was diagnosed in 14 eyes within the Study I period and in 17 and 20 eyes after treatment with the 10-mm and the 15-mm plaque in Study II, respectively. The cumulative incidence of developing radiation maculopathy and maculopathy other than radiation maculopathy were comparable between the two groups in Study II (Table 7). Additionally, the distance of the tumour margin to the center of the foveola (median, 0.5 vs 1.0 mm, *P*=0.23) was comparable in eyes that developed radiation maculopathy.

One eye developed radiation optic neuropathy after treatment with the 10-mm plaque (Studies I and II) of a tumour located at 4 mm from the optic disc. Optic radiation neuropathy developed in 7 eyes after treatment with the 15-mm plaque. The cumulative incidence rates of developing optic neuropathy (Table 7) and the distance of the posterior tumour margin to the margin of the optic disc (median, 4.0 vs 2.0mm, P=0.12) were comparable.

9.1.5. Preservation of visual acuity

A tumour thickness of more than 3.0 mm was associated with more frequent loss of vision, particularly after treatment with the 10-mm plaque, although the number of patients with such a thick tumour was small. Instead, a location of the tumour margin at less than 1.5 mm from the optic disc and foveola was a more prominent indicator for vision loss after treatment with the 15-mm plaque (Fig. 5, Study II). The cumulative incidences of losing a minimum BCVA of 20/65 (low vision) and the development of blindness (BCVA < 20/400) were comparable between the two groups (Table 7).

By univariable Cox regression, low vision and blindness of the tumour eye were associated with a shorter distance to the foveola, a worse baseline BCVA, and larger tumour thickness. Of bivariable models using plaque size, the model including the distance to the foveola independently and best predicted low vision (HR, 0.64 for each 1 mm increase in distance, $P<0.001$; Table 8, Study II). Distance to the foveola was further associated with blindness in a similar bivariable model (HR, 0.68 for each 1 mm decrease in distance, $P=0.004$)

9.2. SMALL METASTASIZING CHOROIDAL MELANOMAS (STUDY III)

9.2.1. Tumour Size and Characteristics

The median thickness of a SFCM at the time of treatment was 2.4 mm (range, 1.0–3.0 mm, Table 8) and its median LBD was 7.3 mm (range, 3.0–9.0 mm). None of the 45 tumours was less than 3.0 mm in LBD at the time of treatment (Fig. 1, Study III), whereas 27% of the 45 tumours ranged from 3.0–6.0 mm and 73% from 6.1–9.0 mm in LBD. Risk factor frequencies (Table 8) at the time of diagnosis were similar to those reported in a study on 35 small melanocytic choroidal tumours that metastasized[27] (Table, Study III).

Table 8. Baseline characteristics and outcomes of 45 patients with a small choroidal melanoma less than 3 mm in thickness, less than 9 mm in largest basal diameter, and who developed metastatic disease.

Age (years)*	57 (26-81)
Treated immediately	31 (69)
Observed for growth	14 (31)
BCVA*	20/40 (counting fingers–25/20)
Colour	
Dark brown	16 (36)
Light brown/amelanotic	24 (53)
Mixed	3 (7)
Distance (mm) (26/45)	
to the foveola*	0.8 (0–5.0) (26/45) †
to the optic disc*	1.0 (0–4.3) (26/45) †
Tumour location	
Temporal	24 (57)
Nasal	18 (43)
Tumour thickness (mm)	2.4 (1.0–3.0)
LBD (mm)	7.3 (3.0–9.0)
US hollowness	26/3/2‡ (31/45) †
Risk features	
over 2 mm in thickness	27 (60) (27/45) †
subretinal fluid	20 (63)
symptoms	37 (84)
orange pigment	21 (57)
margin within 2 DD	24 (92)
margin touching	7 (27)
Primary treatment	
Enucleation	15 (33)
Brachytherapy	18 (40)
Ruthenium^{106}	13
Iodine^{125}	5
Proton beam	11 (24)
TTT	1
Histopathology (20/45) †	
Epithelioid cells	15 (75)
Spindle cells	3 (25)
Extrascleral extension	1
Last status	
Died of metastases	37 (82)
Alive with metastases	6 (13)
Lost to follow-up	2 (4)

BCVA = Best corrected visual acuity; DD = Disc diameter; Data are no. (%) unless otherwise indicated; *Median (range); † (Number of events/numbers at risk); ‡ the acoustic profile lower/equal/higher than the surrounding choroid

9.2.2. Local recurrence, development of metastases, and survival

Local recurrence only occurred after conservative treatment. The cumulative incidence of developing a local recurrence was 17% (95% CI, 7–29) by 5 years and 19% (95% CI, 9–32) by 10 years. By study design, all patients presented metastatic disease. The cumulative incidence of developing metastasis was 51% (95% CI, 36–64) by 5 years and 85% (95% CI, 71–92) by 10 years after primary treatment. The Kaplan-Meier estimate of melanoma-related death following the detection of metastasis was 52% (95% CI, 37–66) at 1 year, 77% (95% CI, 60–88) at 2 years, and 84% (95% CI, 66–93) at 3 years.

9.3. INCIPIENT CHOROIDAL MELANOMAS (STUDY IV)

9.3.1. Baseline characteristics

The median age of the patients was 55 years (range, 41–77) when the tumour was first documented. All tumours were first detected in fundus photographs taken for various reasons (Supplemental text, Study IV). Two patients had fundus photos without a visible tumour. The median tumour thickness was 0.20 (range, 0.15–0.29) mm on OCT. None of the tumours was thicker than the adjacent choroid. The median LBD was 0.52 (range, 0.05–1.09) mm. None of the tumours showed any risk features for malignancy when first documented.

9.3.2. Tumour characteristics at diagnosis

The median time to observe tumour growth before its diagnosis as an incipient CM was 3.3 years (range, 2.2–7.3 years), at a median age of 57 years (range, 47–78) (Fig. 4A). Tumour thickness was unchanged, but the LBD had increased to a median of 1.6 (range, 0.93–2.32) after this observation. All patients had a BCVA of 20/25 (decimal scale, 0.8) or better in the tumour eye, except one patient with a cataract who had a BCVA of 20/40 (decimal scale, 0.5). The median distance to the foveola was 3.7 mm (range, 0.5–5.3) and 2.3 mm (range, 0-6.8) to the optic disc margin (Fig. 4B). The posterior tumour margin touched the optic disc in one eye and extended to within 2 DD of the disc margin in six eyes. One patient had developed four risk features: symptoms, SRF, OP, and tumour margin touching the optic disc. Eight tumours grew symmetrically, including the 2 in the eyes in which a previously normal fundus had been documented. Two patients had a presumed previous nevus that started to grow, of whom one had an asymmetrically growing tumour.

The median growth rate was 0.25 (range, 011–0.72) mm/y corresponding to 34 %/y, which was faster than the growth rate derived from the reference data of 88 growing naevi[43], ($P<0.001$, Kruskal-Wallis test) they were compared with. Restricted to the 7 *de novo* tumours, the corresponding rates were 0.29 mm/y (range, 0.15–0.72) and 55 %/y (range, 24–1437).

The tumour volume doubled at a median of 2.4 (range, 0.95–9.6) times. The median TDT (Fig. 4A) of 609 days (range, 97–1612) for all tumours, and 393 days (range, 97–609) for *de novo* tumours was comparable with the reference data of 194 melanomas[191,192,400,401] (P =0.62, Kruskal-Wallis test).

Excluding the two likely transformed naevi, the predicted interval from the time when the tumour would have been invisible and the corresponding predicted theoretical patient age was 11.7 years (range, 0.6–34.6) and 51 years (range, 32–63), respectively.

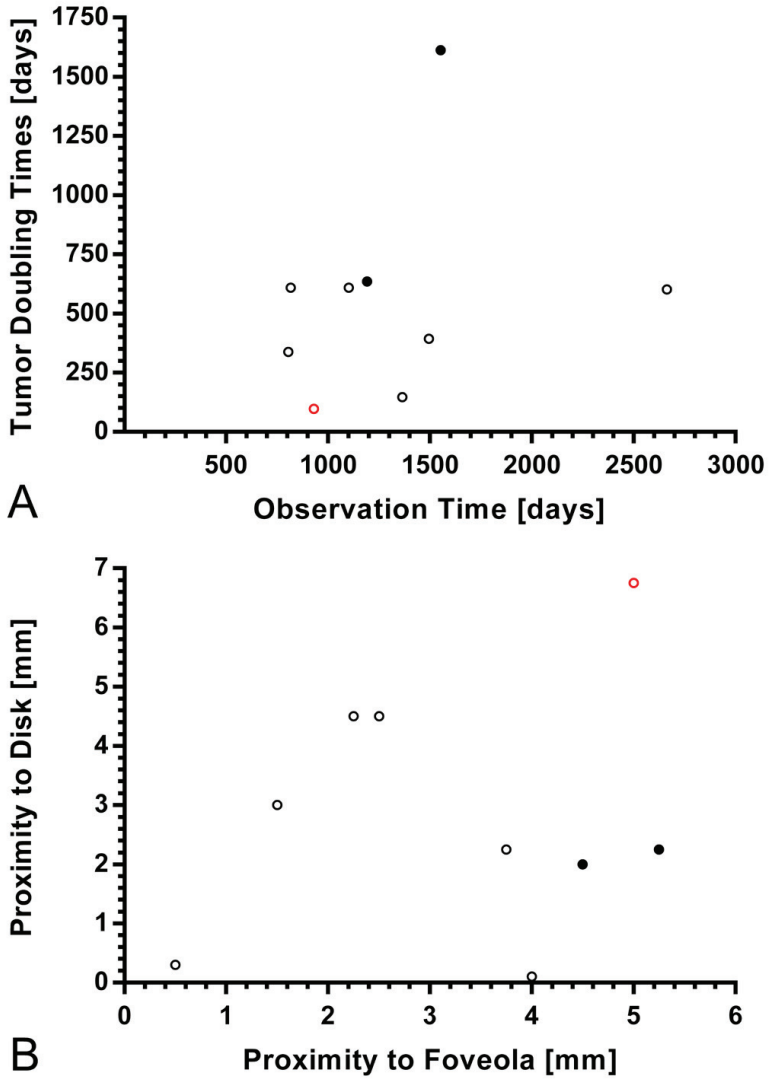

Figure 4. Nine small choroidal melanomas treated with primary transpupillary thermotherapy. **A**, Scatterplot of observation time against tumour doubling time. **B**, Scatterplot of proximity of tumour margin to the foveola against proximity to the optic disc. Solid and open symbols indicate previous naevi and *de novo* melanomas, respectively. Red symbols indicate the tumour of the patient who had a previous T2a, IIa choroidal melanoma.

9.3.3. Transpupillary thermotherapy

One to four (median, 1) TTT applications were applied. Based as well on OCT, the treatment outcome was a white scar with minor RPE remnants in 56% of the patients, a white scar with a focal reactive proliferation of the RPE in 33%, and, as a result of an RPE tear, a scar with prominent reactive RPE proliferations in 1 patient. The median follow-up time after the last TTT session was 2.1 years (range, 7.5 months–8.7 years). None of the patients had developed a local tumour recurrence or metastases within the study period. The BCVA was unchanged in all but two eyes. One patient with a tumour under the papillomacular bundle had a BCVA of 20/40 (decimal scale, 0.5) after completion of TTT. She developed a macular epiretinal membrane and underwent vitrectomy 8 years after TTT. The second patient had a BCVA of 20/125 (decimal scale, 0.16) even after cataract surgery, because of a non-exudative age-related macular degeneration.

10. Discussion

10.1. TREATMENT WITH THE 10-MM OR THE 15-MM PLAQUE

Tumours treated with the 10-mm plaque were more posteriorly located, and the plaque less frequently covered the entire tumour with a safety margin, making these tumours theoretically more vulnerable to recurrences. The observed recurrence rates were low[307,314,315,320,406] and comparable after treatment with both plaques, despite the fact that the 10-mm plaque emits less scattered radiation. While tumours treated with the 15-mm plaque were larger, neither tumour size nor dose to apex was associated with local recurrence in multivariable modelling. An eccentric plaque location was a risk factor for a local tumour recurrence with both plaques, unlike the conclusion in the original paper that reported on the eccentric technique.[310]

TTT has been associated with a relatively high risk of local recurrence with local recurrence rates between 7–45%.[56-59,292] The Kaplan-Meier estimate for tumour recurrence after TTT has been 26% in 5 years[53] compared to a corresponding 9% rate after brachytherapy with the 10-mm plaque in Study I. The number of risk features for growth did not predict local recurrence after treatment with the 10-mm plaque, unlike after TTT.[56] Previous reports advise that small CMs with multiple risk features should be treated with methods other than TTT.[53]

Tumour location likely contributed to tumour recurrences after treatment with the 10-mm plaque. Round eccentric plaques must be used with caution[310] when managing CMs which are located within 1 DD from the optic disc ,where it is possible that a plaque might tilt along the optic nerve sheath. Three of four recurrent tumours in Study I were located less than 1.5 mm from the optic disc. Furthermore, peripapillary tumours have been found to be at a high risk of local recurrence also after TTT.[56,292]

The frequent perifoveal location in these studies explains the high rate of developing radiation maculopathy and thus the effect on reading vision. The unadjusted rate of developing radiation maculopathy was equal with both plaques (19% and 18% at 5 years), as estimated by cumulative incidence analysis, and thus lower than in Study I (28%). The factors associated with a decrease in BCVA were tumour thickness over 3 mm, LBD over 7 mm, and tumour location less than 1.5 mm from the foveola. Although the loss of a minimum vision of 20/65 (=low vision) and 20/400 (=blindness) vision was comparable between eyes treated with the 10-mm and 15-mm plaques overall, multivariable analysis showed that the distance to the foveola, which differed between the two groups, was a factor affecting the risk of vision loss. Controlling for this distance, the risk of losing vision was higher when treating with the 15-mm plaque.

Melanoma-related mortality after treatment with the 10-mm or the 15-mm plaque was not higher than the estimate for small (T1a, stage I) tumours in general[24] despite the fact that a majority of tumours irradiated with the 15-mm plaque were T2a, stage IIA. The 2% melanoma-related mortality in Study I was comparable to that of TTT studies, where metastases developed in up to 5% of patients.[56,57,292,332]

In the literature, a 100% local tumour control has been reported after brachytherapy with the gamma ray emitter Pd^{103} for tumours less than 10-mm in LBD.[407] However, the offset was a higher rate of radiation maculopathy in 43% of eyes and radiation optic neuropathy in 21% of eyes irradiated with Pd^{103}.

Comparable local tumour control and survival rates, as well as a low rate of complications other than radiation maculopathy and relatively good visual outcomes, might favour the treatment of small CMs less than 10 mm in LBD with the 10-mm Ru^{106} plaque over the 15-mm plaque. The local recurrence rate after treatment with the 10-mm plaque appears to be lower compared with TTT[53,56-59,292] and not worse than with the 15-mm plaque when managing patients with a CM less than 10-mm in LBD. Vision loss was more probable after the 15-mm plaque when the tumours were located close to the foveola.

10.2. SMALL FATAL CHOROIDAL MELANOMAS

A total of 3 patients with a small CM of less than 5 mm in LBD who developed metastases were found in the data collected from 10 ocular oncology services in Europe. A CM that metastasized and was less than 3 mm in LBD was not found, which suggests that 3.0 mm could be the limit from which a CM first gains its ability to metastasize, supported by the finding that no tumour smaller than 3 mm in diameter has been reported to metastasize, and the fact that the participating centres did not find any such tumour in a total of over 10,000 treated melanomas. This limit would, however, be subject to challenge and modification if necessary.

This multicentre study further suggests that if the diagnosis cannot be otherwise obtained, it is safe to observe choroidal tumours until they reach 3 mm in LBD in order to verify growth. This will push the size limit for early detection and treatment. Three of the tumours in this study grew over the 3 mm in LBD while being observed, and, on one hand, one can speculate whether metastasis in these patients could have been prevented by earlier treatment. On the other hand, all tumours, once reasonably diagnosed as a CM, regardless of their size, should not continue to be observed but should be treated.

Four percent of the patients in this study did not present high-risk features for growth, and the frequencies of these criteria at the time of their confirmed CM diagnosis were similar to those in earlier reports on small melanocytic choroidal tumours.[27] A comparison of the number and type of risk features for growth between the SFCMs in Study III with those

reported for the unselected CMs in the same size range in Study I suggested that there was no difference. Additionally, the number of risk features for growth has not been associated with a specific GEP class predictive of patient survival.[408] Consequently, according to both this present study and the findings from the literature, no presently known clinical tumour characteristics can predict the development of metastases.

10.3. DIAGNOSIS OF INCIPIENT CHOROIDAL MELANOMAS

All tumours were flat and 2 mm or less in LBD at the time of treatment, which would most likely correspond to the tumour size of a naevus.[31] Only one patient had developed a tumour with 4 high-risk features, and another patient had a tumour touching the disc margin as its only risk feature.[27,42] The diagnosis was based on a verified faster tumour growth compared with that of growing naevi.[43] As these incipient tumours were too small for a biopsy,[149,209-215] they could only be reasonably diagnosed by observed growth. The growth rates reported in this study were higher than those calculated from the reference data of naevi, while the TDTs were comparable with those from the reference data of melanomas, supporting the melanoma diagnosis of these tumours. The patient who had a history of a previously treated ipsilateral CM had the shortest TDT, and, therefore, the possibility of a local tumour metastasis could not be excluded.

It is generally presumed that choroidal naevi emerge during puberty, and that, consequently, new ones should not appear during adult life. For this study, the theoretical age at which each tumour diagnosed as an incipient CM would not have been visible was calculated. With one exception, this age result was 32 years or older. In the reference group from the literature, none of the growing naevi had developed new risk features.[43] Growth of these naevi had been observed in, respectively, 54%, 34%, and 19% of the patients younger than 40 years, 41 to 60 years, and older than 60 years. Five out of the nine patients in Study IV were 47 to 56 years old, while the other four belonged to the oldest group. One of the reference studies including 217 patients with a CMs less than 3.5 mm in thickness identified a patient age over 60 years as a new risk feature for predicting a GEP class 2.[149]

A high local recurrence rate is a concern after primary TTT treatment of CMs when compared with radiation therapy.[52] However, such a recurrence in these incipient tumours would likely be less than 3 mm in LBD and therefore be highly unlikely to metastasize.[61] However, because recurrences have been reported to develop a decade after TTT,[53,56] this study recommends a long-term regular follow-up for these patients, as suggested by other investigators.[53]

A further recommendation can be made that all naevi should be documented, involving mandatory regular check-ups to observe possible changes in lesion sizes. Risk features for the malignancy of choroidal lesions have been reported; however, these features generally develop later in the evolution of the tumour.[4,103] Currently, there is no effective treatment for

metastatic disease, and it is, therefore, necessary to find ways to diagnose and treat patients with CM as early as possible to prevent the occurrence of this fatal event.

10.4. STUDY STRENGTHS AND LIMITATIONS

The Helsinki University Hospital, Department of Ophthalmology, in which this study was conducted, is a national referral center for UMs that offers nationwide data. However, the late follow-up of patients coming from outside the Helsinki region is accomplished in other university hospitals or central hospitals starting 3 or 4 years after treatment if there is no evidence of recurrence. A limitation of all these retrospective studies is that a few patients had partially missing data for their individual visits to other university or central hospitals during their later follow-ups. Additionally, the number of patients in all the studies was small because of the rarity of this disease and the Finnish population amounting to only 5.5 million individuals. This small data set was compensated for by the fact that the present series were consecutive and population-based.

Study II was not randomised, as the plaques were not chosen systematically, and, therefore, the two groups were not entirely comparable. A multivariable analysis was used to adjust for these differences, which aimed at reducing bias. Small CMs are uncommon, making it difficult to organize a prospective study with an adequate sample size or, further, a randomised one.

Conservatively treated patients in all the studies neither received histopathological nor genetic verification, which, however, was in line with the usually reporting for these smallest tumours.

When comparing the results of this thesis for Study I and IV with the reference data in the literature, it is important to take into account the many differences both in inclusion criteria and definitions of complications. A longer follow-up is needed in Study IV to confirm the complete tumour control with TTT.

10.5. FUTURE ASPECTS

It would be ideal to aim for the earlier diagnosis of CM with a diagnostic accuracy of 100% as well as treatment before the tumour reaches metastatic capacity. Choroidal naevi that show no risk features should be regularly monitored and treated when tumours show growth before their diameters are over 3 mm. If the tumours are located outside the posterior pole, they should be treated with less delay. This thesis reports reference rates for tumour growth and doubling times, which could be used for earlier diagnostics. Newer imaging techniques provide new information and show new risk factors for choroidal lesions, aiming at an earlier detection.

It is likely that, in the near future, radiotherapy will remain as the principal treatment option for small CMs. However, an earlier diagnosis could possibly enable the safe use of TTT for extremely small flat tumours despite the criticism against TTT's high recurrence rates for thicker tumours. However, further studies and longer follow-ups are needed to confirm the efficacy of TTT when treating these incipient melanomas.

Metastatic disease constitutes a significant cause of mortality, including in patients with a small CM. It will be necessary, in the future, to detect and manage subclinical distant metastasis to ultimately control this malignant disease.

With earlier local treatment combined with future systemic therapies for subclinical metastasis, the improved survival of patients with UM will be accomplished. Effective local treatment modalities with effective tumour control are available for the appropriate patient selection. However, the prevention of dissemination will be the key to providing the most ideal prognosis. Currently, the most effective measure to minimize poor prognosis is the early detection of CM at a time when the tumour is small, posing the least risk for metastatic disease.

11. Conclusion

I. An acceptable local tumour control, a low rate of side-effects other than radiation maculopathy, and the effective preservation of vision support the use of a 10-mm ruthenium^{106} plaque in treating small CMs.

II. 10-mm ruthenium^{106} plaque contributes to improved visual preservation without increasing the local recurrence rate, particularly with tumours close to the fovea, and may therefore be preferable to the 15-mm plaque.

III. Small CMs of less than 3 mm in LBD are highly unlikely to metastasize, and no known clinical risk feature can predict the development of metastases from a tumour of this size.

IV. Small incipient CMs can be differentiated from small naevi by their growth rates, tumour doubling times, and the calculated age when the tumour originated.

12. Acknowledgements

This study was carried out at the Department of Ophthalmology, University of Helsinki and Helsinki University Central Hospital during the time period from 2011–2020. The research was supported by the Sigrid Jusélius Foundation, The Eye Foundation, the Evald ja Hilda Nissi Foundation, the Mary and Georg Ehrnrooth Foundation, the Foundation of the Eye and Tissue Bank, and the Finnish Ophthalmological Society. I am grateful for this financial support, which has enabled my research. I am grateful to the chief of the department, Jukka Moilanen, MD, for establishing ideal research facilities and for having an encouraging attitude.

My sincerest gratitude is owed to my supervisor, Professor Tero Kivelä, MD. It was summer 2010 when I first contacted Tero Kivelä to ask if I could have a summer job as a researcher aiming to complete my medical licence thesis. Tero Kivelä offered to me a project that aimed toward a doctoral thesis and degree. Possibly due to that interesting offer, I am also specialising in ophthalmology. I could not have received more suitable guidance, teaching, and support during this project. The knowledge and endless hours he provided to this project are more than I could ask for. I am thankful that he guided me through this project and taught me what high-quality research is.

I want to thank my co-writer Rana'a Al Jamal, MD for all the help and support. I further want to thank other co-writers Vappu Reijonen, PhD; Jorma Heikkonen, PhD; Sebastian Eskelin, MD; Virpi Raivio, MD; and Martin Täll, MD.

I want to thank the European Ocular Oncology Group for the opportunity to take part in the collaborative study that our group was privileged to complete. I want to thank all the members who participated in the data collection process and made this exquisite study possible.

It is a truly honour to thank Carol Shields, MD for sharing their unique data set of growing nevi that was used as refence group in the Study IV.

Warm thanks belong to Elina Rantala, MD for all the help, for all the weekends we worked together in the clinic with our own projects, and for demonstrating a hardworking attitude, which I tried to follow. I want to thank Docent Joni Turunen, MD for all the help, and for inspiration to research. I want to thank other doctoral candidates in our research group for support and, most of all, friendship, including Anni Stadigh, MD; Mari Mansikkamäki, MD; Kalle Nummi, MD; Aino Jaakkola, MD; Mamunur Rashid, MD; and Olli Ala-fossi, MD.

I am grateful to Elina Haapaniemi for her endless kindness and helpfulness.

I want to thank my thesis committee members Docent Eeva-Marja Sankila, MD and Docent Mikko Tenhunen, PhD for their support and help.

I want to thank my reviewers, Professor Kai Kaarniranta, MD, and Docent Ann Maria Paula Schalenbourg, MD, for excellent comments as well as constructive criticism.

I want to thank all my colleagues working at the Helsinki University Hospital, Department of Ophthalmology for inspiring, encouraging, and providing me with a respectful working atmosphere for residency and research.

My deepest gratitude belongs to my parents, Eira and Mika, and my brother Niko, who have supported and loved me throughout my life. I am very fortunate to have such a strong and safe background. I am sad that my beloved grandparents never saw me finishing my doctoral degree, although I know how proud they would have been.

Lastly, I want to thank the love of my life, my husband Lauri, who has encouraged me throughout this entire project by supporting, helping, and showing an example by completing his own doctoral degree a few years earlier. He inspires me each day, and it is my greatest luck to share my life with him.

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